Update on CLL | May 1, 2013 • 1:00 PM

Speaker: John C. Byrd, MD

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Slide 1: Welcome & Introduction

OPERATOR:
Hello, everyone, and welcome to ***Update on CLL***, a free telephone/web education program. It is my pleasure to introduce your moderator Mabel Maia of The Leukemia & Lymphoma Society.

MABEL MAIA:
Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you and a special thanks to Dr. John Byrd for sharing his time and expertise with us today.

We have over 1,500 individuals participating from all over the world and many international participants from Australia, Bangladesh, Barbados, Canada, Greenland, Guatemala, Ireland, New Zealand, Philippines, Sweden, and Tanzania. On behalf of LLS, thank you for joining us today.

We would also like to acknowledge and thank Teva Oncology for their support of today's program.

Before we begin, I would like to introduce The Leukemia & Lymphoma Society's President and CEO, John Walter, who will share a few words. John?

JOHN WALTER:
Thank you, Mabel. I would like to add my welcome to the patients, caregivers and healthcare professionals on the program today.

All of us at The Leukemia & Lymphoma Society believe we are living in an extraordinary moment. Our mission is to cure blood cancers, including leukemia, lymphoma, myeloma, and to improve the quality of life for patients.

Since 1954 LLS has been a driving force behind almost every treatment breakthrough for patients with blood cancers and we have awarded more than $875 million to fund blood cancer research.

Our commitment to pioneering science has contributed to an unprecedented rise in survival rates for people with different blood cancers. An important part of our mission is bringing you the latest information about advances in treatment for your blood cancer, so you can work with your healthcare team to determine the best options for the best outcomes.

Until there is a cure, LLS will continue to invest in research, patient support programs and services that improve the quality of life for patients and families.

We are extremely fortunate to have as our presenter today Dr. John Byrd, one of the nation's leading experts in chronic lymphoblastic leukemia or CLL. We appreciate his dedication to supporting the mission of The Leukemia & Lymphoma Society through his research and his care of patients living with leukemia. I would like to thank him for providing us today with an important update on CLL.

Thank you and I'll turn the program back over to Mabel.

Slide 2: John C. Byrd, MD

MABEL MAIA:
Thank you, John.

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MABEL MAIA:
I am now pleased to introduce Dr. John Byrd. Dr. Byrd is the D. Warren Brown Chair of Leukemia Research, Professor of Medicine, Medicinal Chemistry and Veterinary Biosciences. He's also the Director in the Division of Hematology Department of Medicine at the Ohio State University in Columbus, Ohio.

Dr. Byrd, we are so privileged to have you with us today and I now turn the program over to you.

Slide 3: CLL Update on Diagnosis and Treatment

DR. JOHN C. BYRD:
Thanks, Mabel, and thanks, John. And I want to start the program by thanking the Society. We would not be here with some of the things that we're going to be talking about today, that are clearly benefitting our patients. And I would not be here talking if it had not been for the support the Society gave me when I was starting my career, and has continued to support our work. So thank you to the Society from our own patients and everybody on the line.

So over the next 20 or 25 minutes or so, I'm going to give an update on CLL and talk about some of the new and exciting things that are changing. And realizing that everybody on the phone already knows a lot about this, I'm going to start out, though, with some basics, realizing that there are probably family members on the line and, just to be sure, that we're all at the same place.

Slide 4: Chronic Lymphocytic Leukemia
So CLL, as we know, is the most prevalent type of adult leukemia. The disease is defined by flow cytometry, which are markers on the leukemia cells, that are very typical of CLL. Most patients are diagnosed with this when they are older, in their late 60s and 70s. Although a small proportion of people are young. They're 50 years or younger. We see this more common in men, although it obviously can occur in women. And something that's important to all of you to realize is that CLL is a service-connected illness. So if you served in Vietnam or were on a ship around Vietnam, where you were potentially exposed to Agent Orange, this is a service-connected illness, where you can go to the VA and get benefits as well as medical disability from the VA.

A common question about this disease is does it pass from generation to generation. And actually CLL is the most common disease with respect to there being a brother or sister or parent that had it, in about 10% of patients. Although we don't have a common gene right now that has been identified.

Slide 5: Critical Decision Times for CLL Patients
So if we think about CLL, every moment of the disease is critical, but really in terms of making decisions about the disease, there's sort of three critical points: at diagnosis, when you get that call from your internist or family doctor saying, I think you have CLL. Everything ends there. Because you've gotten that dreadful news that you may have something that may shorten your life. And coming to terms with the diagnosis, getting as much information about it and dealing with the watch or wait, which often patients say watch and worry, is a key point. The second sort of important juncture is at the time of first treatment, where you want to have the appropriate tests and the choice of initial therapy. And really at that time considering clinical trials, particularly at this time with non-chemotherapy-based treatment, given the path of new therapies that are coming down the line. And then finally, relapsed disease. Here we need to be sure that you're getting the right tests done and really considering the appropriate treatments, ideally clinical trials in this setting.

DR. JOHN C. BYRD:
And you see at the bottom I've got starred, that all these junctions, while CLL is a disease that's often treated in the community, it's very, very appropriate, at each of these junctures, at diagnosis, times of first treatment and relapse, it's often a good idea to see a CLL specialist, who can work with your local doctor, and so you have two people working on your team that are up to date with things and can coordinate your care in an effective way.

Slide 6: Diagnosis and Evaluation of CLL
When we're seeing a patient with CLL, what's relevant to the diagnosis and evaluation? The immunophenotype or the flow cytometry we said confirms the diagnosis. And with all types of cancers, we have staging. And staging tells us how the disease is going to impact life. And so the higher the stage, the shorter the survival often is. We often use the Rai staging, where zero – and it's denoted on the slide – you just have disease in the blood. Or stage 3 or 4, when you're anemic or your platelets are low. And based upon the stage, that can really impact how your disease is going to behave, whether you're going to need therapy right away.

Bone marrow biopsies and CT scans generally are not needed at diagnosis. They're often done. It's not absolutely wrong to do them. But there's something that probably could be avoided with a good exam and the appropriate blood tests.

Now the staging system for CLL that I have denoted, the Rai staging system, is very good at predicting how CLL patients are going to do in the general population. But for the individual, they're not as good. And some of the new genetic and biologic features such as FISH and IVGH mutational status, which are blood tests that can be done during the first visit, and these are typically the markers that we do when we see people the first time, can differentiate CLL that's going to often be indolent for many, many years, and which may not even result in the patient needing to be treated, versus much more aggressive CLL, where treatment might be needed right away or within the first couple of years, and survival is likely going to be impacted, particularly if it's in a young otherwise healthy patient.

And again, the four prognostic factors that we use when we see people is the FISH, again, looking for the unfavorable deletion 17p, IVGH mutational status, beta-2 microglobulin, and then what happens to the lymphocyte count over the first year. So if it doubles in less than a year, then that goes along with a little bit more aggressive disease. That last one is likely the softest.

There are other prognostic factors such as CD38 and ZAP-70, although these are somewhat less reproducible than the ones that are listed.

Slide 7: Typical Discussion Following Testing
So once we do the testing and we're seeing a patient initially, one generally gets put into a low risk group or high risk group, in terms of how we follow the disease. And ones in the low risk group, where you don't have the IVGH unmutated disease or unfavorable FISH markers, we generally never consider therapy, even as part of a clinical trial. And those patients are typically followed every three months for a year and then six months thereafter. If you have asymptomatic high risk disease, so you have the IVGH unmutated, you have FISH markers that showed the deletion of 11q or 17p, still the approach is not to treat the disease, but it is worthy of considering clinical trials with non-chemotherapy-based approaches that are ongoing at several of the CLL centers. Particularly if you're really having a difficult time with that

DR. JOHN C. BYRD:
concept of not intervening until symptoms develop. And every patient is different in terms of their comfort level with that. And those patients typically that are in the high risk group, we follow every three months indefinitely.

And finally, there's a small group, 10 to 20% at diagnosis who are anemic or thrombocytopenic, and they often need treatment right at the beginning and we generally choose the treatment based upon their genetic features.

Slide 8: Autoimmune Cytopenias of CLL
This is the typical discussion we have when we're seeing somebody and we also go through the complications of the disease that I think are very relevant. One common complication of CLL is autoimmune hemolytic anemia, or ITP, which are low red cells or platelets due to the immune system destroying the normal cells in the blood. And this does not impact on staging, but if it's not treated correctly, people can get very sick. And we generally treat this, both these entities, different than we treat the CLL, often with prednisone, with or without rituximab, and this is something that you can treat and may go away.

Slide 9: Infections in CLL
The other very common complication that we see in CLL is infections. And these are actually the thing that CLL patients have to worry about the most. They cause the highest mortality related to CLL. And things as a patient that you can do is being sure that you get your vaccines right at the beginning of diagnosis, so the Prevnar 13, which is a better pneumonia vaccine, getting this at diagnosis and every five years, getting the flu shot yearly. You should never get a live vaccine, including the shingles vaccine. And if you get fludarabine or bendamustine, particularly as second-line therapy, we generally give prophylactic antibiotics to protect you from unusual infections that the immune suppression from those drugs can cause.

A common question we often are asked because of the cost of IVIG is should it be used. And it is expensive, but for patients that have recurrent infections, because we know the immunoglobulins are low, you can replace that and often get people off of continuous or multiple antibiotic courses for infections that are not clearing.

And similarly, if patients get the flu and have low immunoglobulins, we always replace the immunoglobulins to prevent development of pneumonia.

Slide 10: When to treat CLL patients
So when do we treat CLL? And right now the standard is not to treat patients until symptoms develop, irrespective of whether you have favorable or unfavorable genetic features. And this in part dates back to old studies showing no real survival advantage to treating the disease early, versus at the time that symptoms develop, in terms of survival. In fact, with some of the chemotherapy drugs, there may be complications, such as secondary cancer, associated with treating the disease earlier in the course of the disease.

So for high risk patients now with some of the new targeted agents, this is being addressed in clinical trials, but really outside of a clinical trial, when we see somebody, we really want to derive from them that

DR. JOHN C. BYRD:
they're having some type of symptom from the disease, such as fatigue, enlarging nodes or spleen that are causing discomfort or they're causing early satiety, getting full quickly when you eat, or cytopenias, low hemoglobin or platelets that signify that if we don't treat, it's going to make treatment quite harder.

A big mistake that I often see is somebody's count will go up from 25 to 50 or 50 to 100 and the patient having no symptoms and the doctor will recommend treatment. And really the lymphocyte count as a sole marker of treatment shouldn't really be considered unless it's above 300. And a lot of people get treated based upon a rising lymphocyte count that could be watched for several years often and not require therapy.

Slide 11: History of CLL Therapy: 1970-2013
So how have we treated CLL? And I've sort of outlined the history of CLL therapy. For a long time, we just had the oral agent chlorambucil. Fludarabine was introduced and in untreated CLL patients produced higher response rates, or the disease would go into remission, partial and complete. And the remission would last longer than chlorambucil. However, even though this drug has been around a long time, recent studies have shown that there's not a lot of impact with this therapy for patients who are over the age of 65 and we're moving away from using fludarabine in this age group.

The antibody, which is a monoclonal antibody, rituximab, which was approved in 1997, is one of the first targeted therapies for CLL. And it's an antibody that attaches to the CLL cells and triggers it to die and at the same time it recruits the immune system to destroy it. And when given by itself, it has modest activity in CLL. But when you give it with chemotherapy, you see much higher responses and for the first time ever in CLL, we saw extension of survival. So the treatment, the initial treatment with rituximab plus the chemotherapy, or we often refer to it as chemoimmunotherapy, prolongs survival of CLL patients. And particularly with some of the low risk patients, we see the remission duration is extending beyond ten years.

And so when we look at therapy right now, we would say that FCR or another chemotherapy drug, bendamustine-rituximab, are the standards for young and older patients with CLL. Particularly the bendamustine-rituximab for older patients.

Slide 12: Therapy Approach for Patients (< age 65)
When we consider patients under the age of 65, and they're at the point of treatment, we always do the FISH tests because the FISH tests tell us whether the disease has the genetic marker, the 17p, where people don't respond to therapy. We always will present a clinical trial to patients. And then if they have the deletion 17p marker, our group will use a regimen from Dr. Kipps with rituximab and high dose Solu-Medrol or FCR. If they have the 11q marker, we give FCR or bendamustine-rituximab. And then the other genetic markers, we generally leave the cyclophosphamide out because of the risk of secondary cancers that you see with FCR, particularly secondary leukemia.

Slide 13: Therapy Approach for Patients (> 65 years)
How about patients over the age of 65? I said fludarabine really has not been shown to be beneficial in that group and two combinations that we often use in this patient group is either bendamustine-rituximab or chlorambucil-rituximab. And if it's an 89 year old patient or a 90 year old patient that's really frail, chlorambucil by itself or maybe rituximab are acceptable in this age group. We've got some new exciting options, such as lenalidomide, which is approved by the NCCN, but sometimes insurance companies

DR. JOHN C. BYRD:
don't pay for it. But it's an active immune-modulating agent, so it's a non-chemotherapy drug. It reverses hypogammaglobulinemia, so part of the immune suppression of CLL is causing hypogammaglobulinemia and about half the people that get this Revlimid® can reverse this. And you see less infections with this. And the progression-free survival. So you go on this pill, if you tolerate it well you stay on it, and a great majority of patients who receive this as initial treatment for CLL who are over the age of 65, have extended remissions. So this is one newer therapy that's coming for CLL that's in clinical trials.

Slide 14: Considerations for Relapsed CLL
How about when the disease comes back? And this is where we face our biggest challenge. And really if somebody's being followed in the community, when the disease comes back, particularly after receiving chemoimmunotherapy, this is really where it's important to get a specialist involved. And there are a variety of things that we need to do at that point. We repeat the prognostic factors with the FISH and to see if 17p has shown up because, again, the 17p is a very, very bad actor and pretends that a lot of the standard therapies aren't going to work.

We also consider what therapy people have had. So if they had multiple therapies together, like FCR, and they relapse in a short time period, that's generally associated with not doing well. Whereas if the remission with the first treatment was very long and it was just with one agent, then we would use the same thing.

It's really important, and often doctors don't think of this and patients and their family members can be the best advocate, is that cytopenias or low platelets or hemoglobin can be present at the time of relapse. And in doing a bone marrow, particularly if you've received FCR is very important, because you can find other things, such as myelodysplasia, which will greatly influence how you're treated.

And in general, I still believe that transplant evaluation should be done, if you have unfavorable prognostic factors, but things are really changing and we'll get to that.

Slide 15: Salvage Regimens for CLL
When we think of salvage regimens, I've listed a bunch of things here that can be done that involve chemoimmunotherapy, the FCR treatment, bendamustine-rituximab or high dose methylprednisone and rituximab, or Revlimid or lenalidomide, the oral medicine that I mentioned earlier, plus rituximab. And again all of these are active combinations.

What I would say is the one thing that doesn't work in patients with CLL that's relapsed after traditional therapy, are lymphoma regimens. CHOP, CVP, R-EPOCH, those are not as effective against CLL and they cause a lot of problems with counts and often hair loss. And so that's not something we generally do.

Slide 16: Our Goal in CLL Therapy: CML in 2012
So let's get to the exciting stuff. This shows our goal for CLL therapy. And this is the plot of the progress with CML in terms of survival. And the higher you are to the 1, the better things are. And you see over the decades of CML patients followed at MD Anderson, we've seen a great improvement in overall survival Gleevec® was introduced for that disease, which effectively puts the leukemia in remission. And Gleevec is a pill. I'm sure most of you have heard of it. The diagnosis of CML is made, they're put on this pill, and then they live with their disease. Their disease doesn't necessarily go away where they can stop the\

DR. JOHN C. BYRD:
medicine, but they live with their disease, just like people live with high blood pressure or diabetes or other medical problems, and their quality of life returns to how it was before their leukemia existed.

Slide 17: Targeting BCR Signaling in CLL
In CLL we don't have a common target and this has eluded people for a long time. But it's recently become recognized that B-cell receptor signaling is a target that CLL cells and other B-cell malignancies are very dependent upon. And this is particularly true in the high risk patients, the ones that are the hardest to treat with our chemotherapies, that they're more dependent on B-cell receptor signaling. And we can sort of think about B-cell receptor signaling as the cord going to the lamp, and when you shut this off, the lamp goes off, and we're going to talk about some of the clinical results with some medicines targeting either BTK or Bruton's tyrosine kinase, and PI3 kinase, that have demonstrated this.

Slide 18: GS-1101 (CAL-101) in CLL
One of the exciting drugs that has come into the clinic, is a medicine called GS-1101 or CAL-101. It now has the name idelalisib – and it's a tongue-twister, so I'm going to say GS-1101. And it targets something that B-cells and malignant B-cells are very dependent upon, called PI3 kinase delta. And in the Phase I study, and there's often hesitancy for patients to participate in Phase I studies, but with targeted Phase I studies, using new molecules where we have a rationale that they're going to work, the response is often very high. And in this Phase I study, 54 brave patients participated, some of them are still on this medicine, they had gone through five prior therapies and the majority of them were either deletion 17p or had bulky lymph nodes, 82% had bulky lymph nodes. And in this Phase I study, 91% of people had 50% or greater reduction in their lymph nodes and spleen. But with this class of drugs, we see the cells go out into the blood. So the overall response, blood, lymph nodes, spleen, was 24%. But the patients that had the lymphocytosis in their blood really didn't care for it. And the average remission with this, meaning you go on the pill, your symptoms go away from the disease, was about 18 months. So the responses were very durable. Whereas with traditional therapy we would expect a 20% response rate maybe and a remission duration of six months.

Slide 19: GS-1101 Response and Outcome Summary
In this next slide I summarize some of the information that I told you. In the top of the slide I showed the time of progression and you'll notice that there's still a good number of patients out more than two years that are on the GS-1101 and doing well. This improves hemoglobin and platelet counts if patients start out low. And the only thing about GS-1101 is it doesn't work quite as well in the 17p CLL.

Slide 20: GS-1101 Current Direction
This is currently being studied in several Phase III studies where it's being added to either bendamustine-rituximab or ofatumumab or rituximab. And there will be some up-front studies with this as well.

Slide 21: Ibrutinib (PCI32765) in CLL

DR. JOHN C. BYRD:
The other medicine is ibrutinib. Ibrutinib inhibits Bruton's tyrosine kinase, which B cells are dependent upon. And in our group, had the honor really to be part of a great team of doctors at different centers

DR. JOHN C. BYRD:
here and at MD Anderson and Cornell predominantly, where we tested several doses of this in relapsed patients and in elderly untreated CLL patients, and in 85 patients with treated disease, we looked at two doses, and again most of these had a lot of therapies, a median of four, whereas the elderly patients had no prior therapy. The response in both doses, in the high dose and the low dose, was 92% with about 71% of patients responding by all criteria. So much higher than GS-1101. And at 26 months, 75% of the previously treated patients are still on therapy, still free of disease. In the untreated group, at 26 months, 96% of patients are still in remission doing well. Whereas with our traditional chemoimmunotherapies in that population, it would be about 50%.

The side effects with this oral medicine have been quite modest. We see loose stools, arthralgias, particularly in younger patients, some fatigue, heartburn and rash. We don't really see the counts affected.

Slide 22: Ibrutinib Remissions are Durable
And again, these are the remission duration curves and you see for the untreated elderly patients, it's essentially flat. So people are going on this medicine, they're living with their disease. And even in the relapsed patients, they're doing quite well.

Slide 23: Progression Free Survival by Genomic Feature
The one group where we do see a little bit of relapse is the deletion 17p patients, but you'll notice at 26 months, still more than half of them are in remission. And with 17p disease, even at initial therapy, the average survival is about 20 to 24 months, so they're staying in remission longer than they would be expected to live with other therapies. So this is really a blockbuster drug for all CLL patients. And we're all very excited about this drug.

Slide 24: Combination Studies with Ibrutinib
There are a variety of combination studies that are ongoing with ibrutinib that have shown more activity and these have not added to the toxicity. And we're looking forward to some untreated studies in both the elderly patients and the younger patients, that the U.S. and Canadian cooperative groups will be doing. And there will also be these studies with ibrutinib across the ocean in Europe and Australia.

Slide 25: Where are BTK Inhibitors Going?
Where are these going? As I said, ibrutinib is in a variety of Phase III studies. The big one that compared it to ofatumumab is now closed and we're waiting the results. It's being added to bendamustine-rituximab versus bendamustine-rituximab alone, and then there's a single agent 17p study that's open at several sites for relapsed patients, that's very, very close to accruing.

There are other alternative BTK inhibitors, AVL292, which does have some activity. It does not appear to be as active as ibrutinib to date, although with increasing the dose, maybe it will get to the same point. And then there are other BTK inhibitors with improved features that are coming as a consequence of this.

Slide 26: Chimeric Antigen Receptor (CAR) T-Cells in CLL

DR. JOHN C. BYRD:
I'll finish with the last thing I'm particularly excited about, which are the CAR T-cells, which the Society has sponsored for the University of Penn and David Porter and Carl June have really spearheaded this area. And this is engineering somebody's own T-cells outside of their body and then giving them back, so they can fight the CLL. And this went viral last year with several patients gaining remission. It's a really, really new therapy, but I think it's going to be something in the future that likely replaces transplant.

Slide 27: Other New Drugs (Before BCR Antagonists)
There are a variety of other drugs that we have that are coming forward. Some B-cell receptor inhibitors. Dinaciclib and flavopiridol are both active drugs in refractory CLL. ABT199, which is also a very, very active drug early on, looks as active as ibrutinib, although there are safety issues with it that are going to need to be worked through. And then several monoclonal antibodies, Xm5574, GA101, Tru-016, which is an antibody-like molecule, which all have shown single agent activity. And then lastly KPT330, which is going to be something that's very active likely in Richter's and other B-cell malignancies.

I have starred here that many of these have been supported by The Leukemia & Lymphoma Society.

Slide 28: Important Conclusions
So in closing I'd like to make the point that select genomic studies at diagnosis can help in risk stratifying, telling how your disease is going to do. And it can also help direct therapy. Rituximab added to chemotherapy clearly offers a survival advantage for CLL and we generally use rituximab and add it to something for initial therapy. The 17p patients need a special type of therapy and if you have 17p disease, you need to be seeing a specialist right up front. The BTK inhibitors, particularly ibrutinib, is very active in CLL and I think offers the opportunity to really entirely change the landscape of CLL, where we're not using chemotherapy in the future for this disease, as initial therapy. And then finally the CAR T-cells I see moving forward as having the chance of replacing transplantation for the patients that don't respond to our targeted therapies.

Slide 29: The OSU CLL Team
On this last slide I'd just like to acknowledge our group that's done the work with several of these medicines, GS-1101, ibrutinib and dinaciclib and flavopiridol.

Slide 30: Acknowledgements: Non OSU
As well people at other institutions. And the companies that have developed these B-cell receptor signaling inhibitors. And most importantly, The Leukemia & Lymphoma Society, who have stood by all of our sides to bring forth new therapies for CLL and other types of blood cancers. Thank you.

Slide 31: Question and Answer Session

MABEL MAIA:
Thank you so much, Dr. Byrd, for such a clear and informative presentation.

Dr. Byrd, our first question comes from Diane from the web. "I am a watch and wait patient for the last ten years and my oncologist recently said I have gone into spontaneous remission. Does this happen often?"

DR. JOHN C. BYRD:
That's a great question. It doesn't happen often and you're blessed, but it does happen to a small number of people, usually the low risk patients. And all the data that's available indicates that you will live as long as we would expect you to live without CLL.

MABEL MAIA:
Great, thank you, Diane, for that question. We will take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Sue in New York. Your line is now open.

SUE:
Hi. I'm a patient of Dr. Rai's and I'm getting chemotherapy as we speak. And I know that I'm ZAP-70 negative, which I was told that's good and that I can probably stay in remission for long periods of time. But Dr. Rai said he has a pill that he's hoping the FDA is going to approve. And I wanted to know if you knew about that pill and if this pill will keep me in remission so that I don't have to live with the wait and worry like I did for seven years.

DR. JOHN C. BYRD:
Both of those are great questions. Dr. Rai is correct, in that there are actually two pills, ibrutinib, which I was talking about, and GS-1101, are both pills. And I would say with ibrutinib, from what we know right now, if you're in the low risk group in particular, there's a very, very good chance that if your CLL comes back and you have to go on to ibrutinib, that you'll have a very, very long remission. We're seeing very, very few relapses in the low risk patients with the follow-up that we have thus far. And again, these are both transforming drugs for CLL, particularly ibrutinib, just like in CML, imatinib or Gleevec was a transforming drug for that disease.

MABEL MAIA:
Thank you, Sue, for calling in with your question. Dr. Byrd, our next question comes from Robin from the web. "Are patients with CLL at higher risk of developing skin cancer than the general population?"

DR. JOHN C. BYRD:
That's a great question and the answer is yes. Several studies have shown that both squamous cell carcinomas, basal cell carcinomas and malignant melanoma, and the cause is probably different, but merges on a common theme of sun exposure and the immune system not being intact. And so we always tell our patients when they see us, regarding secondary cancers, is it's important to wear sunscreen, to see if you've had any problem with any type of skin cancer to see a dermatologist twice a year for a detailed exam.

MABEL MAIA:
Thank you, Robin, for your question. Patrick, we'll take the next one from the telephone audience, please.

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OPERATOR:
The next question comes from Robbie from North Carolina. Your line is now open.

ROBBIE:
Thank you very much. I have two related questions. First, I was diagnosed with CLL stage zero about seven years ago. My red blood cell counts and platelets have been stable. My white blood cell and lymphocytes have been stable, however, they've started to increase slightly. My physician has called me a long term slow progressive. I wanted to find out what the actual probability would be in terms of my actual life span. And also in terms of the prognostic factors, how often should they be performed with someone with my particular diagnosis and are there any specific ones that should be performed?

DR. JOHN C. BYRD:
It's hard to say, CLL patients that have low counts without lymphadenopathy, that remain stable for a long time, have a very favorable survival, depending upon their age, might come close to matching the age match population without CLL. The prognostic factors, the four that I've listed on my slide, the FISH, the IVGH mutational, and we do stimulated karyotype as well at OSU, and beta-2 microglobulin, along with LDH and the CBC, those we generally do at diagnosis and then we don't repeat them again until it becomes time for treatment. And the only one, we repeat the FISH, and the stimulated karyotype at the time of treatment because that's really the only one we use to decide therapy. IVGH mutational status doesn't change over time, so it doesn't have to be repeated.

MABEL MAIA:
Thank you, Robbie, for calling in. Dr. Byrd, our next question comes from Paul from the web. "Will there be any clinical trials for someone like myself, age 78, and in stage 4 CLL? My age seems to disqualify me from many clinical trials."

DR. JOHN C. BYRD:
My apologies for trials excluding you because you are in the age group where CLL is most common. And the new study that I mentioned, comparing ibrutinib to ibrutinib plus rituximab to bendamustine plus rituximab, does not have an age cutoff and you would be eligible for that. And the ibrutinib versus chlorambucil study that Pharmacyclics is doing right now, you would be eligible for. And really most of the trials that are done at CLL centers of excellence don't have an upper age cut. We often have a cut if you can't walk into the clinic and you're not functional, because then it becomes hard to know if giving the medicines are going to be safe, particularly if it's a more aggressive treatment. But there are trials and it may just be getting to a CLL center of excellence to have the opportunity to participate in one of those.

MABEL MAIA:
And Paul, to add to that, you can also feel free to call our Information Resource Center, where you could speak to a specialist about further information about clinical trials. And I will give that number at the end of the program. Thank you, Paul.

I will take the next person by phone.

OPERATOR:
The next question comes from Jeanette in Florida. Your line is now open.

JEANETTE:
Yes, I was wondering if any more had been done about the vaccine for CLL that they had worked on at MD Anderson several years ago and haven't heard any more about it.

DR. JOHN C. BYRD:
I think you're referring to the Genitope vaccine?

JEANETTE:
They had said originally that it was a vaccine for CLL that would also help people who had CLL and then suddenly I didn't hear any more about it.

DR. JOHN C. BYRD:
So the biggest vaccine study that's been done in asymptomatic CLL is the Genitope vaccine, which is a vaccine to something called the idiotype, that's unique to the CLL cells. And that trial was performed in asymptomatic patients and there's not been much said about it. Its success in low grade lymphoma was not evident.

Now you lead into a very interesting topic that we're most excited about it, is that the medicine that we talked about earlier, Revlimid or lenalidomide, and ibrutinib as well, where we're coming to recognize both have the ability to turn off the immune suppression that's seen in CLL and in lymphoma. And so revisiting these studies with vaccines in CLL with these new targeted agents is likely going to be something that's considered in the future. So there's really not a lot out that's been successful with those past studies, but the exciting thing is is that they may have a rebirth with some of these new treatments and the ability of these new treatments to sort of accentuate potentially the vaccine response.

MABEL MAIA:
Thank you, Jeanette, for calling in. Our next question comes from the web from Mia. "You said lenalidomide is approved by NCCN. Is that different than when a drug is approved by the FDA?"

DR. JOHN C. BYRD:
That's a great question. To begin, for the record, I'm not a paid consultant for Celgene or take nothing from Celgene, so when a drug gets approved for use in a disease, through the FDA, it goes through the rigors of the FDA looking at all of the data from the clinical trials. The NCCN is a group of experts that review the clinical data that's available with a drug that's already approved and if there's ample evidence, generally we require two or three or more clinical trials in a given area, and if the results look positive and the safety is very, very good, then drugs that a company has not necessarily put through the rigorous FDA review, which costs a lot of money, we will say that this is a reasonable thing to do for CLL. And so it's a practice guideline that community physicians use, but it's not FDA approval. That's a more rigorous process. But again, there are a lot of drugs that are used in cancer care that are not necessarily FDA approved, but where there's really good data to support using them. And Revlimid or lenalidomide,

DR. JOHN C. BYRD:
there's more and more data coming forth, that it is a very active and worthwhile therapy for CLL. I am on the NCCN committee and every drug that we look at across all blood cancers and solid tumors is looked at very, very rigorously, but again, differently than how the FDA does.

MABEL MAIA:
Thank you, Mia, for submitting your question. We'll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Jim in Washington. Your line is now open.

JIM:
My wife is a CLL patient for 13 years. She sees Dr. O'Brien in Houston. And I just wondered what's the significance of milk thistle seed extract driving the white count down from about 160,000 to about 30,000, over a period of a year? Are there any studies on this?

DR. JOHN C. BYRD:
That's very interesting and I don't know of any studies on this. But it sounds like you've got a great CLL doctor at MD Anderson and that maybe you've identified the next green tea.

MABEL MAIA:
Thank you, Jim, for calling in with that question. Our next question comes from the web from Dan. "Please address the clinical relevance of minimal residual disease as it applies to CLL survivors and post-chemo follow-up monitoring and/or re-intervention."

DR. JOHN C. BYRD:
Okay, so that's a three part question. When we treat CLL with chemotherapy or chemoimmunotherapy, it's when we do very sensitive tests. The CAT scans and flow cytometry, very sensitive flow cytometry on the bone marrow. And we find that there's no evidence of CLL. We find no evidence anywhere in the body that somebody has CLL, then we would say that they're minimal residual disease negative after treatment. And with chemotherapy or chemoimmunotherapy such as FCR or bendamustine-rituximab, that correlates with much longer time that you're in remission, and a much better survival. So that's something at the end of therapy where you want to be if you're getting chemotherapy.

Now the question is, is it a marker of the disease being favorable or is it actually something that we should act on. And so if you go through therapy and your MRD is positive, then it's still really a research question because generally most of the time people are asymptomatic at that point. And there's not a definitive study showing that if you add therapy at that point, that you improve survival. That's a research question.

And so MRD in some is something that's useful to tell how you're going to do, how long your remission is going to last after therapy. It's not something where it's imperative to treat.

DR. JOHN C. BYRD:
The last part that I would say is everything that we've learned about minimal residual disease or MRD with chemoimmunotherapy is probably totally irrelevant to these new drugs, the BTK inhibitor and to the GS-1101, because they produce very sustained remissions, even if there's MRD present. And so these older concepts with chemotherapy may go out the window as we identify and move these new active non-chemotherapy approaches forward for the treatment of CLL.

MABEL MAIA:
Thank you, Dan, for submitting that question. We will take another one from the telephone audience, please.

OPERATOR:
The next question comes from Ted in Wisconsin. Your line is now open.

TED:
Hi. I'd like to know what is the preferred treatment for a senior who had multiple therapies for the last four years with low platelets and low white count? Thank you.

DR. JOHN C. BYRD:
I would say for any patient that needs to be treated, a clinical trial is the ideal thing. And I would say for people with relapsed disease, the trials with the B-cell receptor antagonist, either ibrutinib or GS-1101, are the most active drugs and we find ourselves at OSU trying to get our patients to those trials.

In terms of standard therapy that's available for patients that have low counts, really a lot depends upon the genetic makers of the CLL, and really if you get past the first line of therapy, it's really important to involve a CLL specialist that really deals with the disease and that can really look at the individuality of your case and come up with a plan that matches your person in the appropriate manner.

MABEL MAIA:
Thank you, Ted, for calling in with that question. Dr. Byrd, our next question comes from the web and it comes from Helen. "First, thank you so much for sharing your info and doing this program for all of us. My question is this. There are drugs that sometimes state that they may affect your immune system. People that have weakened immune systems may have increased risk of developing infections. Given CLL affects our immune systems, should we avoid taking any meds with that warning label? If not doing chemo at the time, should we still avoid these meds? Are our immune systems compromised whether doing or not doing chemo or any treatment?"

DR. JOHN C. BYRD:
All of our traditional chemotherapies, so fludarabine, particularly fludarabine, bendamustine, steroids, suppress the immune system and the chemotherapies that we use, suppress the immune system for a long time. The disease suppresses the immune system as well. And so when people start out at the point of needing therapy and they get chemotherapy or chemoimmunotherapy, they're often at their most immune-suppressed point. And as the disease is knocked down, there's more immune suppression, but it actually gets better with time as the disease goes away because the disease can promote a good bit of immune suppression.

DR. JOHN C. BYRD:
What's really exciting about the targeted drugs, I would say ibrutinib, the GS-1101 and lenalidomide, is when you start patients on them, they do still have problems with infections because their immune systems are compromised from the disease. But you don't see added immune suppression from what they had from prior to starting therapy, and then as you move on, you actually see components of their immune system get better. And I think that's why we're seeing that patients that get the immune-modulating agents or the kinase inhibitors are doing so well over an extended period of time, because we're not impairing the immune system as much. I hope that answers your question.

MABEL MAIA:
Thank you, Helen, for that question. We'll take the next from the telephone audience, please.

OPERATOR:
The next question comes from Trudi in New Jersey. Your line is now open.

TRUDI:
Yes, hello, Doctor. I'm a 60 year old woman and I was diagnosed at 53 with CLL. Had a bone marrow biopsy and aspiration. It was 40% in my bone marrow. My white cells at the time were 18 and they're now at 36. With my lymphocytes I believe at 17. I also have chronic sinus problems, angioneurotic edema and ulcerative colitis. Does this affect my CLL in any way? Also recently my cholesterol has gone pretty high and I want to know if that has anything to do with the CLL.

DR. JOHN C. BYRD:
The association of ulcerative colitis or Crohn's disease is not very common, although we have seen a small number of patients with both diagnoses. And I think where it becomes complicated is if you need therapy for your CLL. Most of the therapies for Crohn's or ulcerative colitis either have no effect or may have a positive effect on the CLL.

TRUDI:
Okay. And would that affect the cholesterol as well?

DR. JOHN C. BYRD:
It shouldn't.

TRUDI:
Okay. And you did mention something earlier about the genetics. Can this be handed down to my children? My son, who was recently diagnosed with Crohn's.

DR. JOHN C. BYRD:
So CLL has a genetic component. If a brother or sister has had it, or a parent, a first degree relative. If you don't have that history, then it's likely you have sporadic CLL where there's less of a chance of passing things down. And similarly, inflammatory bowel disease, either ulcerative colitis or Crohn's, there can be a familial component to it. That's about all I know and what I remember from my residency relative to Crohn's.

MABEL MAIA:
Thank you, Dr. Byrd, and thank you, Trudi, for calling in with that question. Our next one comes from the web from Susan. "You talked about the drug ofatumumab. Is it the same as the drug Arzerra®?"

DR. JOHN C. BYRD:
Ofatumumab is the same thing as Arzerra and it's a new CD20 antibody that probably, very likely in my opinion, and we'll see what the results of the randomized trials are, is better than rituximab. And there's a third CD20 antibody called GA-101 that's completing clinical trials right now, so we're lucky that we have three CD20 monoclonal antibodies. Because as I said, CD20 monoclonal antibodies are one of the therapies that we've seen to prolong survival with CLL patients.

MABEL MAIA:
Thank you, Susan, for that question. We'll take the next one from the telephone audience, please.

OPERATOR:
Our next question comes from Luis in New York. Your line is now open.

LUIS:
Hi, Dr. Byrd, thank you for the call today. I'm recently diagnosed here at New York Presbyterian. I was given stage zero diagnosis and I'm on a three month watch and wait. Haven't gone for my first follow-up yet. But I have two questions. One is right now the most significant symptom I have is anxiety. And I've been looking for ways to manage it. But I was just wondering, first of all, stage zero, but the anxiety associated with it nonetheless, is there anything that you recommend? I started drinking green tea, I started trying to meditate and pray a little bit more, but frankly the anxiety is worse than anything, because I don't have symptoms.

DR. JOHN C. BYRD:
First of all, I'm sorry that you've gotten this news and you're experiencing anxiety. And I think many of the people on the phone, if they could speak, would agree that this is, particularly for younger people, but young and older people, this diagnosis brings on a lot of anxiety. And what I tell my patients is one way to get through the period of this stress and get your hands around the idea of watching and waiting, is getting as much information about the disease and educating yourself. And often as you educate yourself and you get information about your disease and you learn, well, I have the favorable genomic markers, there are all these great therapies, and I will say there's no good leukemia, there's no good time to be diagnosed with CLL. I wish everybody on the phone had not been touched by this disease. But the times we're in right now are the most promising that we've ever had. That looking to the future, I've been telling many of my patients, particularly like you, that it is very, very, very likely that even if you get to the point of needing to be treated for your CLL, you will not have to have chemotherapy. These new drugs are going to potentially greatly impact how we treat CLL and I firmly believe that we will not be using any part of chemotherapy for a treatment, moving forward after these next set of trials that I've outlined, have completed. So that's what I would say.

DR. JOHN C. BYRD:
The other couple of things, is that if there are things that you don't like doing, that are causing stress, use the CLL as a reason to get rid of them. A patient of mine who I'm blessed to take care of, I've learned more from him than I think I could ever do for him, talks about his CLL being a positive thing, that it's a blessing, once he's gotten his hands around what you're talking about, because it's allowed him to sort of refocus on what's important and made him a much happier person.

Slide 32: LLS Resources

MABEL MAIA:
Thank you, Luis, for calling in with your question. And actually, thank you all for all your questions. Our program has come to a close. We hope this information will assist you and your family in your next steps.

If we were not able to get to your questions, please call The Leukemia & Lymphoma Society Information Specialists toll-free at 1-800-955-4572. Or you can also reach us by email at infocenter@lls.org. Our specialists can provide you with information about CLL research and clinical trials and other questions you may have about treatment and financial assistance.

There were many questions about choosing a specialist today. We at LLS have a fact sheet called Choosing a Blood Cancer Specialist or Treatment Center, which you can call our Information Resource Center to get a copy, or you can download it from our website at www.LLS.org/resourcecenter.

Please help me thank Dr. Byrd. We are so grateful he has donated his time with us today.

And on behalf of The Leukemia & Lymphoma Society, Dr. Byrd and I would like to thank you for sharing this time with us. Good-bye and we wish you well.

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