

Information for Patients with Chronic Lymphocytic Leukemia

May 19, 2016

Speaker: Susan O'Brien, MD



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Slide 1. Welcome & Introductions

OPERATOR:

Greetings, and welcome to *Information for Patients with Chronic Lymphocytic Leukemia*, telephone and web education program.

It is now my pleasure to introduce your moderator Lizette Figueroa-Rivera. Thank you Ms. Figueroa-Rivera, you may begin.

LIZETTE FIGUEROA-RIVERA:

Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, I would like to welcome all of you.

We have over 1,200 people participating from across the United States and several countries around the world, including Canada, India, The Netherlands, Sweden and Switzerland.

Special thanks to Dr. Susan O'Brien for sharing her time and expertise with us today.

Before we begin, I'd like to introduce Dr. Lee Greenberger, our Senior Vice President and Chief Scientific Officer of Research from The Leukemia & Lymphoma Society, who will share a few words. Lee, please go ahead.

DR. LEE GREENBERGER:

Thank you, Lizette. I'd like to add my welcome to the patients, caregivers and healthcare professionals attending the program today.

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is simple: it's a world without blood cancers.

For more than 60 years LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved the survival rates and quality of life for many blood cancer patients. To date we have invested over \$1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program demonstrates, we are a leading source of free blood cancer information, education and support, and we touch patients in their communities throughout our 56 chapters across the United States.

LLS also acts as a voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them to navigate their cancer treatments, and ensure that they have access to quality, affordable and coordinated care.

We are very fortunate today to have as our presenter Dr. Susan O'Brien, one of the nation's leading experts in leukemia. She is the Associate Director for Clinical Science for the Chao Family Comprehensive Cancer Center and Medical Director for the Sue and Ralph Stern Center for Cancer Clinical Trials and Research, based at the University of California in Irvine. She has been the lead investigator for over 40 clinical trials and has authored over 600 journal articles as well as numerous book chapters and she is truly an expert in the field.

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DR. LEE GREENBERGER:

We appreciate her dedication to supporting our mission and her commitment to caring for patients living with blood cancers. I'd like to thank her for providing us today with important information for chronic lymphocytic leukemia, and I'd like to thank you all.

And now I'll turn the program back to Lizette.

LIZETTE FIGUEROA-RIVERA:

Thank you, Lee.

And we would like to acknowledge and thank for their support of this program Genentech & Biogen, Gilead, Infinity Pharmaceuticals, Pharmacyclics & Janssen and an educational grant from Teva Pharmaceuticals.

I am now pleased to introduce Dr. Susan O'Brien from the Chao Family Medical Comprehensive Cancer Center in Irvine, California. Dr. O'Brien, I'm so privileged to turn the program over to you.

Slide 2. Information for Patients with Chronic Lymphocytic Leukemia (CLL)

DR. SUSAN O'BRIEN:

Good morning, everyone. I'm going to give you a little bit of background on CLL, the disease, and then we're going to spend most of the time talking about the available treatment options that there are.

Slide 3. Disclosures

This is my disclosure.

Slide 4. What is CLL?

So what is CLL? CLL stands for chronic lymphocytic leukemia and as you all know it's a type of blood cancer that as you can tell by the name, involves lymphocytes, which is one component of the white blood cell system that helps fight infections. The other one is neutrophils.

So what happens in CLL is that the lymphocytes are not normal and they build up in the blood and in the bone marrow and sometimes if the bone marrow, which is where you make all of your normal blood cells, gets extensively involved with CLL, this can kind of crowd out the normal cells and you can wind up with anemia, which is low red blood cells, or low platelets, which are the part of your blood that help your blood clot. So people can have bleeding problems or symptoms of anemia with fatigue or shortness of breath, etcetera.

Infection is also a common problem in patients with advanced CLL because of the fact that again normal white blood cells are not completely normal, the lymphocytes are not, and also many of the treatments we use, and I'll talk about this, can sometimes lower the other white blood cells, the neutrophils that help us fight infection.

In addition, the lymphocytes can build up in the lymph nodes so you have what we generally refer to as swollen glands, and they can also enlarge the spleen.

Slide 5. What are the symptoms of CLL?

DR. SUSAN O'BRIEN:

So what are the symptoms of CLL? Well, actually many people are diagnosed without having any symptoms. And I would say that there's two common ways that people get diagnosed. A very common one is they're going to their physician for a routine physical and they have some blood tests done and the blood tests show that the lymphocyte count is elevated. So that's very common. Those people may have no symptoms at all.

Another way that people sometimes get diagnosed is that they themselves might notice an enlarged lymph node, particularly in their neck. Think about how many times during the day you touch your neck or scratch your neck and so you might develop a lymph node and find it that way, but otherwise have no symptoms.

As time goes on and the disease builds up, people can have symptoms. They can have tiredness, shortness of breath, particularly if they're anemic, a low grade fever, night sweats. The signs of the disease are that the lymphocyte count is elevated, sometimes the lymph nodes increase in size as I mentioned, the liver or the spleen can also increase in size, and again, if the CLL is crowding out the normal cells, you can get anemia or low granulocytes or low platelets.

Slide 6. Understanding medical tests for CLL

So you can't diagnose CLL just by symptoms, but usually you have a physical exam because the doctor is going to check for any enlargement of your organs or swollen lymph nodes, the blood count, as we just talked about. You may or may not need a biopsy of your lymph nodes. If the blood count clearly shows an elevated white blood cell count, we can usually make the diagnosis from doing tests purely on the blood, and people don't necessarily need to have a lymph node biopsy.

Flow cytometry again is a test that we do on the peripheral blood lymphocytes to determine if they're malignant or not. Sometimes people have X-rays or CT scans to look at whether they have lymph nodes, say, in their abdomen, which are often very hard to feel, as opposed to in the neck or under the arms or in the groin, where the doctor can usually easily feel them because they're superficial.

Slide 7. Patients with CLL have a median age at diagnosis of 71 years and most have comorbidities

Now this tends to be a disease of older people, the median age being 71. Median means about half the patients are over that age and half are younger. That's what a median is. So you can see that some people can be quite old with this disease, late 70s, 80s, even I've had patients in their 90s. One of the relevant points about this, the fact that people do tend to be older, is that we know as people age they have more comorbidities, so what's a comorbidity?

Slide 8. Coexisting medical conditions - Effect on treatment approach

Basically any kind of other medical problems. So hypertension, diabetes, atrial fibrillation or an irregular heartbeat, COPD in people who've smoked, any of these would be considered a comorbidity. And you all know that in older people, you know, these kind of things accumulate over time.

So the relevance of this is that up until recently all of our treatments for CLL, which I'm going to talk about, were chemotherapy-based. And so the bottom line is in an older patient and particularly an older patient with a lot of comorbidities, it's much harder for them to tolerate chemotherapy.

DR. SUSAN O'BRIEN:

So the German CLL Study Group actually developed this sort of way of approaching patients, again, at a time when all of our treatments were chemotherapy-based, which as we'll talk about is not true anymore. So there were what they called the Go-go patients, these patients might be older but they didn't have comorbidities, they had a normal life expectancy, they were in really good shape, people that go to the gym a couple of times a week. Then they defined the term Slow-go and these were people who had some comorbidities or some impaired organ function like maybe some kidney dysfunction, for example, and there they would take a less aggressive approach with the chemotherapy regimen. And then the group that they called No-go, which would be has very elderly frail patients, in bed most of the time, really not in any shape to take any kind of a therapy. And again this was based on the fact that up until recently all of our treatments for CLL were chemotherapy-based.

Slide 9. Chemoimmunotherapy: Chemotherapy and Antibody Regimens

So if we look at the chemotherapies that we have and nowadays they're pretty much all what we call chemoimmunotherapy, that means chemotherapy is given with what's called a monoclonal antibody and the antibody is not a chemotherapy per se, but it's a protein that's designed to bind or attach to the CLL cells, and when we give it with chemotherapy it facilitates the killing of the CLL cells by the chemotherapy.

So the regimen that we would give to the Go-go patients in general is a three drug regimen called FCR, which is two chemotherapies, fludarabine and cyclophosphamide, and then the antibody here is rituximab.

For people who are kind of Slow-go but go, we're not talking about the really frail patients, they would get bendamustine and rituximab, or if they're bordering on frail, although still pretty functioning, they might get a chlorambucil-based regimen. So chlorambucil being a milder chemotherapy than either the combination of fludarabine and cyclophosphamide or bendamustine, and there there's two different antibodies, which are generally used, obinutuzumab or ofatumumab.

So the theme is a chemo, and I'm showing you them here kind of running from the most aggressive, if you will, to the least aggressive on the slides, all of them given with an antibody.

Now what do I mean by aggressive, what's the problem if you take a stronger chemotherapy? Well, some of its side effects, like nausea, etcetera. But the biggest risk is actually not the direct side effects of the chemotherapy. It's that chemotherapies are simply not that specific for the CLL cells. So you also get some killing off of normal cells. So if you start chemotherapy, your red blood cell count is going to drop initially, your platelet count is going to drop, and your granulocytes, which are the key white blood cell that fights infection, are also going to drop. And that's just a known side effect of the chemotherapy.

If your granulocytes drop, the biggest risk is developing an infection and that is probably the number one complication of any chemotherapy in CLL, is the risk for developing an infection.

Slide 10. Why Not Treat CLL at Diagnosis

Now CLL is kind of an unusual leukemia because it's probably one of the – it's not the only leukemia, but we don't necessarily treat people at the time we make the diagnosis. So you might say, well, why don't we treat them? Well, many of them have very slow moving disease. In fact, some people, about 25 to 30%, never need treatment for their disease and they die of other causes that people die of as they get older – another cancer, heart disease, stroke, etcetera.

DR. SUSAN O'BRIEN:

We already discussed the fact that many people don't have any symptoms, so why bother to treat them if they feel fine. This is again an older population, on average. We already talked about the fact that they have comorbidities and again you have an 80 year old who has a lot of other medical problems and very minimal CLL, it's a good bet that they're not going to die of CLL. And if they're asymptomatic they don't need the treatment. And most patients are not cured, although some may be.

Now somebody who's thinking about it could say, well, Dr. O'Brien's not really making any sense because we know that the paradigm in cancer therapy is you've got to get in there and get it early, that once it's more advanced of course you can't cure it. So why would we be doing this, why would we be waiting, people have more advanced disease and are more symptomatic before we would treat them?

Slide 11. Survival: Daily Chlorambucil Versus Observation

Well, because there were a number of clinical trials done in the 1980s, and this is one, and I'm going to explain this curve to you in a second, where the clinical trial asked the question will earlier treatment in people who are otherwise asymptomatic be more beneficial than our standard strategy, which we still use, which you're all familiar with, which is watch and wait. Or some people say watch and worry.

So this was a randomized trial, meaning half the patients were assigned randomly like the flip of a coin to receive chlorambucil, that mild chemo that we talked about, or to observation until they have progressive disease. Okay? Let me explain what this is. This is a survival curve. So every time a patient dies the curve drops down, alright? And what you can see is that we're starting out with everybody alive and over time people do die, not necessarily of CLL, but as we discussed, other causes. But the important point I'm trying to make here is that there's no difference in these curves. They're basically superimposable.

So this said, well, you know what, early treatment did not cause people to live longer. Now somebody could say to me, well, don't you think today in the year 2016 there are better treatments than chlorambucil? And yes, there are. But this is where back in the – and these trials were done in the 1980s, there really wasn't anything but chlorambucil. And so this led to the policy of watch and wait, which may change now with newer drugs, but is still the policy that everybody follows.

Slide 12. Types of Response in CLL

Since we're going to talk about treatment of CLL, I wanted to talk about the types of response that you can get to treatment. So basically once a patient gets treated they can either have no response, and that's pretty obvious, I don't think I need to explain that, but that's not very common. Most people will show some sign of a response to treatment, particularly if it's their first treatment. That kind of response can either be a partial remission, and again is a little bit intuitive. That means that the disease clearly got better, the blood counts improved, the lymph nodes or the spleen shrunk down, they're not very enlarged, but they didn't go back to normal. So it's only partial. A complete remission means the exam is normal, the blood counts are normal and the bone marrow is normal. So obviously that's a better response than a PR.

Now you may hear the term used of whether the response is MRD positive or negative. So MRD means minimal residual disease and that's a very sensitive test to look for CLL when we otherwise can't see it. So in other words, your average MRD test can detect about one in 10,000 cells, obviously way beyond our ability to see the cell in the blood or in the bone marrow.

DR. SUSAN O'BRIEN:

So in general, the better the response the longer it lasts. So a complete remission will last longer than a partial remission, and then a complete remission that's MRD negative, meaning where we can't even detect one in 10,000 cells, is generally very, very durable and significantly longer than a CR where we have MRD positivity.

Slide 13. Other Important Definitions Related to Clinical Trials

So two other important definitions that are going to come up, when we talk about the outcomes of clinical trials in terms of the various treatments. One is progression-free survival. So let's say the patient responds to treatment and they're in remission. Now we're trying to look at, well, how does that remission last? So on a progression-free survival, shows how many patients are in remission, the disease has not come back and alive. If somebody dies of something else the curves drops down or if they lose their remission the curve drops down. We're trying to see how many people are still alive and in remission.

Overall survival, basically if you're looking at it within a clinical trial, it starts at the time of the trial and measures how many people are still alive or not.

Slide 14. CLL10 Study: FCR VS BR in Front-Line

So a recent clinical trial that was done asked the question is FCR or BR better? I told you that they're both a little more aggressive in terms of their impact on the blood counts as opposed to chlorambucil. And some people like FCR and some people like BR because some doctors thought, well, FCR I think is a bit more toxic, but it's a better treatment. And others said, well, BR is a pretty good treatment and I like to use it because it's less toxic.

Slide 15. CLL10 Study: FCR VS BR in Front-Line (cont.)

So this is a trial the Germans did where they randomly assigned people, again, like the flip of a coin, to get FCR or BR. And this is a progression-free survival curve. So again let's go over it. You're looking at 100% at the start, time zero, everybody who's in remission. And as soon as somebody comes out of remission or dies, the curve drops down. Okay? So what you can realize is the further out the curve is, the better the curve, alright? So for example, we look at the 50% mark and we draw a line across, we see that at three years about 50% of the people who got BR in the green curve are still in remission. But if we look at the blue curve and draw a line across from 50% and then draw the line down, it looks more like it's almost five years. So obviously the blue curve is better than the green curve and this showed that the remissions last longer with FCR.

Slide 16. CLL10 Study: FCR VS BR in Front-Line (cont.)

Well, was there any price to pay? Well, there was. As expected, FCR produced more low neutrophils and again that puts you at risk for infection, 84% of the patients developed a very low neutrophil count, grade 3 to 4 means quite low, versus only 59% with BR. And the P value is telling you whether this is a statistically significant difference. So the lower the P value, the more significant it is. So this is very significantly different, but the truth is the numbers are so different you could have figured that out without the P value.

DR. SUSAN O'BRIEN:

If we now go down and look at infection, and again when you have low neutrophils your biggest risk is infection, you see that 39% of patients who got FCR had a grade 3 or 4 infection. So that's not just a minor infection like a cold or something, that's something like pneumonia or generally something where the patient has to be hospitalized. And only 26.8% of people who got BR had a bad infection.

So FCR is a better regimen, but BR is more well tolerated. So a lot of times people will choose whether to use FCR or BR, depending again as we talked about, on the age and the comorbidities of the patient.

Slide 17. CLL11 Study Design

Now at the same time that trial was being run, comparing the two more aggressive or myelosuppressive chemotherapies, FCR and BR, this trial was being done with chlorambucil, which as I told you is a very mild and oral chemotherapy drug. This was also a randomized trial, but in this trial there were three arms. So the patients could be randomly assigned to any one of the three arms. And that was chlorambucil alone, chlorambucil plus GA 101, which is now called obinutuzumab, that's one of the antibodies I put on my earlier slide, or rituximab and chlorambucil. So the initial analysis was saying if we add an antibody to chlorambucil does it make it better.

Slide 18. CLL11 Study Design (cont.)

And then the secondary analysis was asking which of the antibodies is better.

Slide 19. Progression-Free Survival (Head-to-Head)

So what we saw is that either antibody improved the outcome of patients compared to chlorambucil alone. So again this common theme that antibody makes chemotherapy better. But we see in this curve, and remember I told you the curve that goes the farthest out is the better one, and here you have the dotted arrows drawn in to point out for you, so with chlorambucil and rituximab, about half the patients have lost their response by 15 months, whereas with obinutuzumab and chlorambucil, it took over a year for half the patients to lose their response. So clearly the obinutuzumab was better with chlorambucil at least, than rituximab, and the FDA (U.S. Food and Drug Administration) approved that combination regimen.

Slide 20. Phase III COMPLEMENT1: Ofatumumab + Chlorambucil vs Chlorambucil Alone

There was a similar trial going on in Europe, mostly in England, that was a two arm trial. So again these tend to be older patients receiving their first therapy. They were randomized to receive chlorambucil or chlorambucil and that other antibody I mentioned earlier, ofatumumab.

Slide 21. Ofatumumab + Chlorambucil vs Chlorambucil Alone: PFS*

And so here we don't have the rituximab arm for comparison. Just chlorambucil versus chlorambucil and antibody. And again helpfully for you the dotted lines are there. With chlorambucil alone about half the patients had lost their response by a little over a year, but with ofatumumab and chlorambucil, it took almost two years for half the patients to lose their response. So clearly that is a very effective regimen and that is also FDA approved for treatment of CLL. But again chlorambucil is generally reserved for people who would not tolerate FCR or BR.

Slide 22. Targeting of BCR Signaling in CLL

DR. SUSAN O'BRIEN:

Now probably what you've all heard about are some of the newer drugs that have been approved in the last two to three years that are very exciting drugs. They're exciting because they're not chemotherapy, so they don't have the same side effects that chemotherapy does and they don't have the same risk for infection. They're oral, so people like that, they don't have to come in and get intravenous therapy like they do with FCR or BR or even with chlorambucil, because although chlorambucil is oral, the antibodies given with it are intravenous. People kind of like the concept that they won't have to come in for IVs.

And the two I'm going to mention today are what are called B-cell receptor, that's BCR here, inhibitors. So what's the idea here? This is a CLL cell, okay. If you activate this receptor on the surface of the cell, it's transmitted down, down, down into the nucleus, okay. The nucleus is what's below these dotted lines on the bottom, alright. So that tells the cell grow and it helps to proliferate and survive. Well, we don't want that to happen in CLL. So the idea is here we're going to try and interrupt that signaling. We're going to take one of these enzymes, which are also called kinases, just a fancy word for an enzyme or a protein, and we're going to try and inhibit them, okay? And if we inhibit this, maybe the message won't be able to be transmitted downstream to the nucleus and the cell won't thrive because we're interrupting this messaging.

So there's three actual enzymes that have been targeted and I circled them with red circles. But the two drugs that are approved are ibrutinib, which targets BTK, and idelalisib, which targets PI3K. We're going to talk about those two drugs.

Slide 23. Ibrutinib in Refractory CLL With 11q Deletion

So one thing that we see when we use ibrutinib, and I'm going to talk about that first, is that we get very, very rapid reduction in lymph nodes. So you can see this is a patient of mine and I didn't even have to examine him to see how big his lymph nodes were because you can see them jutting out there on the left. And after four weeks of taking ibrutinib once a day, they were almost completely gone. So very rapid and dramatic responses in the lymph nodes.

Slide 24. Pattern of Response: Blood Lymphocytes vs. Lymph Nodes

But at the same time that's happening, and these are the lymph nodes in the SPD on the right, you can see that dramatic drop down in the lymph nodes, and they continued to decline over time, what you're seeing on the right is the absolute lymphocyte count, the ALC. That means the lymphocyte count in the patient. Wow, look how much that goes up. That's because what this drug also does is interfere with certain other proteins that keep the cells adherent inside the lymph node. So we're actually getting initially this rush of cells out of the lymph node into the peripheral blood. Now the good news is people can walk around with very high lymphocyte counts and generally be asymptomatic. So we don't worry about this too much, but it's important to recognize it because if you're a patient and you're getting the drug and this starts to happen, you may panic and think whoa, what's going on here, my lymphocyte count is going up. But that is the way the drugs work. What you can see is that it peaks at about one to two months and then gradually comes down over time, so that later the lymphocytes and the lymph nodes and the peripheral blood become normal, if you have a complete response, but that can take several months.

Slide 25. Ibrutinib Phase 2 Best Response (Investigator-Assessed)

DR. SUSAN O'BRIEN:

So this is the most long term data with ibrutinib now and there were two groups of patients that were treated in this trial. This was not a randomized trial. Everybody got ibrutinib. This group where it says TN were treatment-naive. So these are people who had never had chemo, but they were needing therapy for their disease and they were all 65 years or older. The RR stands for relapsed/refractory patients, which is the second bar, so these are people who've had other treatments, had other chemotherapies, but the disease has come back. And then the last bar is just the composite of both the first two bars.

So the one thing that you can notice when you read the bar graph is, and it helps you out here by giving you the number at the top, is that wow, response rates are really high to this drug. So 85% of the treatment-naive group responded, 94% of the people who had failed chemo. So very high response rates with ibrutinib.

Slide 26. Progression-Free Survival

Now we come back to our progression-free survival curve. The blue were the treatment-naive patients, so not unexpectedly they're doing better because they haven't become resistant to chemotherapy. They're a more untreated group to start with. You can see that there's only one blip down on that curve, that's one patient who lost their response rather early. And you can see if you look at the bottom on the legend that we're out at 36 to 42 months, all the way to the right. And if you look at the blue curve, you can see those little tick marks towards the end of the curve, those are people that are still on treatment. So the point is most people are still receiving this drug out over four years now, and they haven't lost their response. Only that one patient lost their response early. So that's pretty impressive.

If we look at the yellow curve, those are the relapsed/refractory patients, still doing really well, we're out 42 months, 60% of them are in remission. The average number of prior treatments that this group had had was four. If we had tried to give these people chemotherapy we would have been lucky to get three or six months out of it because they were so refractory to chemotherapy already. So this is really a phenomenal finding. So not only are the response rates high, but these response rates are quite durable.

Now do they last ten years? Don't know. Because what I just showed you is the most recent follow-up. This generally gets updated every year at various scientific meetings and we'll probably get an update of that data this year. But we don't have ten year data or fifteen year data like we do with chemo, and I'm going to come back to that point at the end.

Slide 27. Ibrutinib: Common AEs (All Grades, Regardless of Causality)

So this is another bar graph, except it goes out to the right, and basically the numbers at the bottom tell you how many percentage of patients have the side effect. So you can tell the bar that goes out the furthest is diarrhea, so that's the most common side effect, right at the top there. But is generally mild, grade 1 to 2. You can see the grading by the color legend on the bottom. No grade 4s anywhere. And it's usually self-limited. Meaning many people get very mild diarrhea when they go on, but then they keep on the drug and it actually goes away.

Slide 28. RESONATE™ Phase 3 Study Design

DR. SUSAN O'BRIEN:

So then there was a randomized trial because the FDA generally wants a company to prove that their drug is better than a standard drug to approve it. So this is a randomized trial where people were randomly assigned, again flip of a coin, to ibrutinib, what's now the standard dose of 420 once a day, or ofatumumab, the antibody.

Slide 29. Progression-Free Survival

And what this showed is that the remissions were much longer with ibrutinib and now you can see how dramatically different these curves are. So clearly better than a standard antibody.

Slide 30. Safety: Atrial Fibrillation and Bleeding-Related Adverse Events

Now one thing we did find out from that trial, however, is that if you look at the atrial fibrillation, I mentioned that earlier, that's an irregular heartbeat. Ten people on ibrutinib developed that and only one on ofatumumab. Well, obviously that's a big difference. So this trial led us to recognize that there's a small percentage of patients who developed an irregular heartbeat on ibrutinib. And as you can see from the text, many had predisposing factors like a history of atrial fibrillation in the past, or high blood pressure or some kind of heart disease.

The other side effect that is very common with ibrutinib is bleeding-related – AEs, by the way, just stands for adverse events. However, the bleeding is generally very minor, petechiae or ecchymoses, ecchymoses is nothing but a fancy word for bruising. So you can see that 44% of people who got ibrutinib do develop bruising. You know, unless you're going in a beauty contest, bruising is not that big a deal. Only 12% developed it on ofatumumab, so yes, bleeding is somewhat more likely with ibrutinib, but if we look at the severe or major bleeding events, they were quite rare, only two with ibrutinib and three with ofatumumab, and so serious bleeding is a risk, but it's a very low incidence risk.

Slide 31. Idelalisib is an Orally Bioavailable Small Molecule that Inhibits PI3K Delta Potently and Selectively

Okay, let's talk about idelalisib. That's the other agent that inhibits PI3K delta. A different enzyme, but in that B-cell receptor pathway. This drug is also dynamite at shrinking lymph nodes and very rapidly.

Slide 32. Marked Reductions in Peripheral Lymphadenopathy Were Observed

Again you can see the massive amount of lymph nodes that this woman had in her neck, and how they all disappeared on idelalisib treatment. So extremely impressive and very rapid reductions in lymph nodes with this drug also.

Slide 33. Idelalisib: Nodal and Overall Response Rate

If we look at the response rate, and this was the original Phase I trial, meaning where they were testing different doses, but everybody got idelalisib, 81% of them had reduced their lymph nodes over 50%. So in the same kind of ballpark as what we saw with ibrutinib. But the lymphocyte count, which went up, if you look over at the right, as expected, and then slowly came down, kind of plateaued with this drug. It didn't really look like it was going all the way back to normal. And so the company decided to develop this drug with antibody, just like we use antibody with the chemotherapy. So although ibrutinib is

DR. SUSAN O'BRIEN:

approved as a single agent, idelalisib is approved with rituximab and I'm going to show you the trial that led to the approval.

Slide 34. Idelalisib: Adverse Events ($\geq 15\%$) and Selected Lab Abnormalities (N = 54)

So these are the side effects. This first column of numbers is grade 1 to 2, so mild. And the second column is grade 3 to 4, so more severe. And you can see that more severe side effects are quite rare with this drug. The bottom where you're looking at the text under laboratory abnormalities, AST and ALT are liver tests that we do in the peripheral blood. People can have elevated liver tests and feel fine, so that's not a side effect that necessarily bothers anybody, but it's a common side effect with the drug.

Slide 35. Study 116: Randomized, Double-Blind, Placebo-Controlled

So the trial that led to the approval, and again I told you the FDA likes randomized trials so they can see that the new drug is better than some kind of standard. This was a trial of rituximab and idelalisib versus placebo and rituximab. So the people were either getting idelalisib or placebo. If they responded to rituximab and then lost their response, they were actually allowed to cross over. So in other words, if people were randomly assigned to placebo, had a response to rituximab by itself but then lost it, they could actually get idelalisib.

Slide 36. Primary Endpoint: Progression-Free Survival

Again if we look at the progression-free survival you see that the blue curve looks a lot better than the red curve. Very dramatic improvement in progression-free survival, compared to rituximab alone. And that is what led to the approval. But as I mentioned, it's a combination.

Slide 37. Venetoclax: Potent and Selective Bcl-2 Inhibition

And the last drug I want to talk about that literally just got approved by the FDA about two weeks ago, but for a specific indication, that is for patients with relapsed CLL with a 17p deletion. We didn't talk about this, but some of you probably know that 17p deletion, which is a chromosome abnormality that can be present in the CLL cell, generally makes those cells quite resistant to chemotherapy. So patients with 17p deletion do respond to ibrutinib and they do respond to idelalisib and rituximab, but they respond very poorly to chemotherapy. Meaning that before we had these new drugs, those patients had very poor outcomes and shortened survival because of the inability to respond to chemo.

Venetoclax is not a B-cell receptor inhibitor. This is a BCL-2 inhibitor. BCL-2 is a protein within the CLL cell that's very elevated in CLL and it helps keep the cell from dying. It's an anti-death protein. So if we could lower the levels of BCL-2 we might be able to induce death of the CLL cell. So this is also oral, but works a little bit differently.

Slide 38. Dosing Schedule of Venetoclax: Dose Escalation Schematic

This drug, we don't start with the full dose. The original schema on the top is how it was started, it was given initially in the clinical trials, and then the schema at the bottom is the current one and the FDA approved one. So you can see if you look in those green boxes that we start with a test dose, 20, and then we potentially go to 50 and then 100 and then 200 and then 400, which is the target dose. So once people get to 400 they stay on 400 indefinitely. And I should really mention, and I'll come back to this

DR. SUSAN O'BRIEN:

right at the end, that with all these oral drugs they are given indefinitely, so we keep people on them until they either lose their response or they develop a toxicity where they can't take them anymore.

Now why do we have this stepped up dosing schema with venetoclax? Because with venetoclax the side effect that we see is tumor lysis. For those of you who don't know what tumor lysis is, it's kind of a mixed bag. Physicians like when they see tumor lysis because what that means is the drug so rapidly decreasing the amount of leukemia that the cells are breaking open and kind of clogging the blood. However, if you have bad tumor lysis, it can clog your kidneys and lead to heart arrhythmias and to death. So it could be a very risky side effect.

So the way we get around it is we use this slow stepped up dosing, rather than giving the whole 400 right at the beginning, where we would have massive reduction of the cells all piling into the bloodstream and potentially causing tumor lysis.

Slide 39. Best Percent Change from Baseline in Blood Lymphocyte Count and Nodal Mass by CT Scan

This is a plot which shows you on the left the lymphocyte count, how much they go down. This is called a waterfall plot and you can kind of see why. Each one of these lines is a separate patient and what you can see at the top there, it says median time to 50% reduction in the lymphocyte count is two weeks. That means if you have a patient who started with a white blood cell – a lymphocyte count at 200,000, in only two weeks they're already down generally to 100,000. So very rapid declines in the white blood cell count. At the same time, what I'm showing you on the right, are the lymph nodes. The average time to 50% reduction in the lymph nodes is 1.4 months, so a little over – about five weeks. So the point I'm making here is unlike the B-cell receptor inhibitors, ibrutinib and idelalisib, where initially the lymphocyte count goes up while the lymph nodes shrink with this drug everything shrinks down very rapidly at the same time. Both the lymphocyte count and the lymph nodes. That's why this drug has a risk for tumor lysis, because everything is coming down very, very fast and potentially clogging up the bloodstream and the kidneys and causing tumor lysis. So that's the reason for the stepped up dosing here.

Slide 40. Objective Responses of Venetoclax Treated Patients

In the original trial that was done, venetoclax had an overall response rate of 77%, if you look at that first column, and you can see that in patients with deletion 17p, the high risk group I mentioned, which the next column is, 79% of them responded. So a beautiful response rate in patients with deletion 17p. And with this drug you can see about almost a quarter of the patients actually developed a complete response. Keep in mind that all these patients that had prior chemo, and on average of four prior chemotherapy regimens, to see a complete response, meaning we can't see the disease, in a patient who's failed four chemo's, is pretty darn impressive. So another highly impressive drug. And we also sometimes see minimal residual disease negativity with this drug.

Slide 41. Minimal Residual Disease (MRD): Preliminary Analyses

Now all of these drugs have been approved for treatment relapsed CLL – ibrutinib, idelalisib and rituximab, and venetoclax with the stipulation for venetoclax that patients not only have to be relapsed, they have to be 17p deleted. But I'm going to talk about this slide in a second.

Slide 42. RESONATE™-2 (PCYC-1115) Study Design

DR. SUSAN O'BRIEN:

So what does it mean if that's the reason, the FDA approval? Well, once a drug is approved a physician, an oncologist, could give it to anybody they think would benefit from it. So yes, it could be approved for recurrent CLL, if you're a patient who hasn't been treated yet, you might be saying, well, okay, but I'd kind of like to get that before I get chemotherapy. Well, the problem is that although the physician can prescribe it to you, nobody prohibits them, the insurance has to pay for it. And I will tell you that these are all expensive drugs and as I already mentioned to you, patients stay on them indefinitely, as in years potentially. So what insurance companies may do, and it varies a lot from insurance company to insurance company, is say, well, the FDA did not approve this as initial therapy, so you can take it if you want, but we're not going to pay for it. So that's one of the ways in which the FDA – what the actual FDA approval was for is very important because it has a big impact on what will get paid for. Again nothing wrong with a doctor prescribing a drug that's FDA approved for whatever they want to prescribe it for, but with a very expensive drug the other important component of the question is, will it get paid for?

The reason I'm bringing this up now is none of these drugs had what we call a front line approval until very recently. So ibrutinib is the only one that now has a front line approval, meaning it can be used to treat people who need treatment, mind you, but have never seen chemotherapy. And this was based on a randomized trial again, as I told you the FDA likes, where people were randomly assigned, never been treated, they were all over the age of 65. Why? Because we talked about the fact that in older people with CLL it's much harder to give chemotherapy.

Slide 43. PFS by Independent Assessment

So these patients were randomly assigned to get the standard doses of ibrutinib, 420 milligrams once a day, until PD, which is progressive disease, or toxicity, or to get the old standard chlorambucil. What we saw in this trial, in these untreated patients who are getting ibrutinib as their first therapy, is that it was way better than chlorambucil. Look how high up that curve is. Over 80% of people are still in remission at about two years with ibrutinib versus less than half with chlorambucil. So that's what led to the approval.

Slide 44. Overall Survival

And in fact there was a survival advantage over chlorambucil. And let me stress that, people. This is a randomized trial compared to a very weak chemotherapy agent. You might say to me, well, I'm a fit healthy person and I wouldn't be getting chlorambucil, I'd be getting, if I need treatment, FCR or BR. What about compared to that? Right now we don't have any data. There are clinical trials being done across the U.S., looking at – two different trials – looking at the comparison of ibrutinib to BR. And another trial looking at the comparison of ibrutinib to FCR. And some of you may be on those trials, but we don't have any data from those trials yet. So what we can absolutely definitely say is ibrutinib is much better than chlorambucil. Is it better than FCR or BR? That we don't know yet. That's an important point. Because if you weren't going to get chlorambucil in the first place, then, you know, how does this trial help you? Well, you can get ibrutinib because the FDA approval was not age-restricted. So if you're in great shape and you're 55 and you need treatment, you can get ibrutinib. The question, and I'm going to address this in one minute right at the end, is how do you decide, since we don't have data yet.

Slide 45. FCR300: Progression-Free & Overall Survival

DR. SUSAN O'BRIEN:

This is long term data from MD Anderson, where FCR was developed, looking at long term outcomes with FCR. And if you look at the bottom there at the months, you see how far out this curve goes, out to about 14 years. This is really, really long term data. And what we see, if we look at this blue curve, is that there's a subset of patients who out 10 to 14 years, are still in remission and don't seem to be relapsing, i.e. raising the question could these people actually be cured. They're not relapsing because you see that plateau on the curve. It's not falling any more. So does this actually represent a subset of patients in the circle that might be cured?

Slide 46. FCR300: PFS by IGHV Mutation Status

Well, MD Anderson's investigating that right now, but the question is, even if they're not cured, wow, they got six months of chemo and I should stress that, I'm going to address it in my last slide, they're done, they're not on pills, they're not taking anything, and they're still in remission 12 years later. Do we know who those people are to some extent? The IGVH-M at the top here that tells you that's what that blue curve is, those are people who have a mutated IGVH gene. So if we take all-comers with CLL, about half of them have this mutated gene and half don't. The ones that don't still get pretty good remissions with FCR, that's what you see in the red curve, you know, they're lasting years, but they're losing their remissions over time because that curve keeps dropping. Whereas the mutated group, wow, they might actually have a cure fraction.

Slide 47. Oral Small Molecules in CLL

So to summarize in my last two slides, ibrutinib is FDA approved, now it's approved for both initial therapy and relapse therapy. Although the randomized trial was only done in patients for initial therapy, was only done in patients over the age of 65, where chlorambucil would be a standard versus a more intensive chemo, the FDA did not limit the approval. So it just said physicians can use it as initial therapy without any restriction on age.

The question I'm going to address in the last slide is if you're a young person, how do you decide if you want to take chemo or ibrutinib.

Idelalisib is approved in combination for rituximab with recurrence, and that is not going to be developed as a front line therapy.

And then venetoclax I told you is also approved for patients where the disease recurs, but specifically for the group that has 17p.

Slide 48. Considerations for Ibrutinib vs Chemoimmunotherapy as Initial Therapy for CLL

Now my last slide I wanted to give you some considerations for what you should be thinking about as a patient if you're young and/or fit and you're coming up on needing therapy and you're trying to think, well, should I ask my doctor if ibrutinib is better, and obviously you need to discuss it with your doctor, or should I get FCR or BR?

Well, here are some considerations. Ibrutinib is a pill. Chemotherapy is IV. Very big difference is a defined time on therapy. FCR or BR is six months. Chlorambucil-based chemo can be six to twelve, but no longer than twelve. Ibrutinib is indefinite, as we've already talked about. Three pills a day indefinitely.

DR. SUSAN O'BRIEN:

A great drug, but you take it indefinitely.

What about long term results? You might say to me, well, Dr. O'Brien, you showed me that long term data with FCR, show me the long term data for ibrutinib. Well, we don't have long term data, the drug is too new. We have maybe four or five year's follow-up, the most. Certainly not talking about cure. Could there be a fraction of patients that are cured? Of course there could be. We just don't have the long term follow-up to know that.

With FCR – and by the way I showed you the MD Anderson data, but there are two other recent publications showing the same thing, that a subset of patients with FCR are still in remission well over ten years, and again they just got chemo for six months.

Cost is an issue. Chemotherapy-based treatments, generally insurance pays for the whole thing. Oral drugs, most patients have some kind of copay. I mentioned that these are very expensive drugs, but companies generally have assistance programs, but some people don't qualify for them and you may not be, you know, below the poverty line, but your copay be a significant amount of money on a drug that's quite expensive.

So I think that this is something that you obviously need to discuss with your doctor, if you're young and fit and coming up on needing therapy. You know, these are all considerations that have to be taken into account and you need to get your doctor's advice.

What I didn't mention here is the choice of therapy might depend on the status of the CLL like the mutation status. But again this is something that needs to be discussed with the physician. I'm just showing you here things to consider until we have the data from those randomized trials, comparing ibrutinib to FCR or to BR.

And I think that's my last slide and I'll give it back over to Lizette.

Slide 49. Q&A Session

LIZETTE FIGUEROA-RIVERA:

Thank you so much, Dr. O'Brien, for your very comprehensive and very friendly overview of CLL. It is now time for the question and answer portion of our program.

And we'll take the first question from our web audience. Dr. O'Brien, Kathy asks, for those affected with CLL that are women, is it true that they are more likely to experience chronic fatigue and what can a person do to deal with this?

DR. SUSAN O'BRIEN:

I don't think women are more likely to. I think men can get chronic fatigue also. Fatigue is a tricky symptom because it's a vague symptom, okay. I know plenty of people, sometimes myself included, who don't have leukemia who are fatigued. So one thing we do is, when I'm talking to a patient who really doesn't have much other disease, so their volume of disease is low, and they don't have any other symptoms but fatigue, it's important to make sure that there's no other causes for the fatigue. Because what happens is sometimes people assume, okay, I have leukemia, that's why I'm tired. That's not always true, particularly if you have very little CLL.

DR. SUSAN O'BRIEN:

So for example, I will always check somebody's thyroid. About 20% of the American population develops low thyroid and that's a very common cause of fatigue. I'll check testosterone levels in men. Vitamin D levels. There's a variety of reasons why people can be fatigued. Am I saying it can't be from the CLL? No, it absolutely can be from the CLL. But the point I'm making is if the fatigue is such that we're going to actually initiate treatment, we want to be sure that the fatigue is coming from the CLL because we don't want to give somebody therapy that they don't need. But if fatigue is a major problem that can be an indication for treatment of the underlying disease.

LIZETTE FIGUEROA-RIVERA:

Thank you for the question, Kathy, and thank you, Doctor. Our next question comes from the telephone audience, please.

OPERATOR:

Our next question comes from Richard from New York. Please state your question.

RICHARD:

Yeah, hi. I was just given ibrutinib and I haven't started taking it because I have a little sore throat. I had a tooth extraction on May 4th. And my ear hurts and my throat hurts. I called my oncologist and they want to see me tomorrow. But I just wanted your opinion on it, should I see an ear, nose and throat specialist (ENT) to perhaps rule out any infection? And if I have a little infection, say a sore throat, should I postpone the treatment until the infection – until the soreness goes away?

DR. SUSAN O'BRIEN:

I think that your oncologist is being reasonable, usually with CLL there's no urgency to treat, and we generally don't like to put a new treatment on somebody having a problem. We generally like to wait until the problem's resolved. So I think that's quite reasonable. The ENT, I mean I think you have to see your doctor in general and if he feels it's out of his realm he can refer you to a specialist. I think that's something you have to consult with your doctor about. But I think just delaying the treatment a bit until the infection resolves is quite reasonable.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And the next question comes from our web audience. Fred asks, I'm six years out from last treatment and in remission. Is it normal to still have night sweats and enhanced senses?

DR. SUSAN O'BRIEN:

Well, night sweats can also be caused for other reasons. So for example in women, obviously hot flashes, etcetera can occur during menopause, and for many years afterwards, so again that's not always CLL. In men if testosterone levels go down as they get older, sometimes they get sweats. And some normal people have some degree of sweats. So again some of these symptoms, even sweats, are rather nonspecific and not always associated with the CLL, but they can be. So if somebody is in remission and doesn't have any evidence of disease, I would be looking for some other cause for the sweats.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And our next question comes from our web audience. Daryl M. asks, are there any trials for stage zero patients and are our children or siblings at risk?

DR. SUSAN O'BRIEN:

Well, let me take the second part of the question first. In about 5% of patients with CLL it tends to run in the family. But it doesn't run in the family like blue eyes or brown eyes. You may have someone who has it and then their children don't have it, but their cousin has it. So there are people, though, where CLL seems to run in the family. But again they only account for about 5% of the total population that gets CLL. So the simple answer for the most part is no, your children don't have to worry about anything. But if you have multiple other people in your family that have it, then you may be one of those CLL families. There's a lot of research going on at the NIH on what's going on there, where it tends to run in families, but we don't actually know in those families why that happens.

Are there any trials for stage zero? Well, I know a lot of trials in the U.S., but I cannot claim to know every single trial there are. The LLS might actually be able to help you with that question. I understand where you're coming from. I had mentioned earlier in the talk that we take the watch and wait strategy because trials done in the 1980's did not show a benefit to initial treatment with chlorambucil. Well, obviously ibrutinib is a much better drug than chlorambucil, you saw that from the randomized trial that I showed you, and it's a much more effective drug. So the question would be should be redoing those randomized trials, taking people and giving them ibrutinib if they're asymptomatic, or watch and wait and asking the same question, but now updating the trial to the 21st century, where we have better treatments.

I'm aware of a trial in Germany asking this question. I don't know in the U.S. For those of you who don't know, I think LLS is very helpful in assisting people with finding trials. But off the top of my head I do not know if there's a trial in the United States specifically for early stage asymptomatic people.

LIZETTE FIGUEROA-RIVERA:

Yes, Dr. O'Brien, we do have an Information Resource Center and our Information Specialists, which you can contact by phone or online, will be able to do personalized clinical trial searches for you and I will give the information for them later on this call.

We'll take the next question from our telephone audience please.

OPERATOR:

Thank you. Our next question come from Trudi from Florida. Please state your question.

TRUDI:

Yes, hi. I have two questions. One is it usual for people that are diagnosed with CLL to have angioneurotic edema? And the next question was with CLL, the CLL, ulcerative colitis and angioneurotic edema, is there a connection there?

DR. SUSAN O'BRIEN:

So some people with CLL do get what we call paraneoplastic syndromes and often those are autoimmune, so the type of things that is being described, the angioneurotic edema, which is more or

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DR. SUSAN O'BRIEN:

less hives, and the ulcerative colitis, outside of CLL, those are autoimmune conditions. So in other words they're conditions where for whatever reason the person's own immune system kind of attacks them and causes these side effects. So in ulcerative colitis obviously inflammation of the colon and angioneurotic edema, well, basically swelling, sudden swelling, like of the lips or the mouth or whatever. There's not a specific association with either of those with CLL, except in the sense that paraneoplastic syndromes, and there are many of them, can be associated with CLL. So that's the best I can tell you on that. If you say to me is there a known association, say, with ulcerative colitis, no. But there are people who get kind of unusual autoimmune manifestations that may or may not be related to the CLL.

LIZETTE FIGUEROA-RIVERA:

Thank you. And the next question, Doctor, comes from the web. Deena asks about white blood counts, how high before overt symptoms occur?

DR. SUSAN O'BRIEN:

Generally we don't want symptoms to occur, so we will intervene before that. What I mean by that is probably the complication that we would see with a really high white blood cell count, and it varies a bit from person to person, but I'm going to say in general you wouldn't see it below 600,000. Although I wouldn't let somebody's lymphocyte get that high, but let me explain to you.

So what happens is if you get really high lymphocyte counts, 700,000, 800,000, 900,000, a million, I've actually seen patients come in with a million that were undiagnosed, but it's rare, think about how many cells are in your blood. So what's happening? Your blood is like sludge to some extent. So any place there are small blood vessels, particularly the brain, it's hard for the blood to circulate, so people can get dizziness, they can get confusion because the blood flow is so impacted in the small vessels. They can have a heart attack if it's a coronary vessel that gets plugged. So you don't want the white count to go up that high.

Generally we would treat with a lower white count, but I will tell you that people who only need treatment because of their white count are quite rare. I've seen them, but to a large extent the lymphocyte count goes up, the nodes enlarge, and a bigger problem than the actual lymphocyte count itself is that – and you can imagine this – if the lymphocyte count is getting up that high, the bone marrow's pretty much overtaken. So the bigger problem in which we do want to intervene well before the lymphocyte count is in the hundreds of thousands, is that people start to get anemic or their platelets go down, and that's a clear indication for therapy. We don't want people to be anemic, short of breath, fatigued, bedridden, etcetera.

So in my experience it's not the higher the lymphocyte count that generally determines it, it's the fact that as it gets higher and the disease advances, the red blood cells or the platelets start to drop and that's when we intervene.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And we'll take the next question from the telephone audience, please.

OPERATOR:

Thank you. Our next question comes from Gloria from Wisconsin. Please state your question.

GLORIA:

Is it okay to take something like curcumin or MSM, glucosamine sulfate, with ibrutinib?

DR. SUSAN O'BRIEN:

I know a lot of people do like to take those types of things. I'm unaware of any interaction with them, but there are certain drugs that do either generally raise the levels of ibrutinib if they're taken with it. A very common one is antifungals. So the point I'm making is that I don't know off the top of my head for every drug, but it is definitely something, if you're going to start yourself on something, to discuss with your doctor. Because there are agents that can interact by like making the levels higher, so you'd be in effect taking a higher dose. There are actually some, although this is less common, that can cause the levels of ibrutinib to go down, and so you may be getting an ineffective dose. So that's a very important – I'm unaware of anything for curcumin specifically, but any time you're going to take a new agent, whether it's over-the-counter or a prescription, you absolutely need to discuss that with your doctor before you start.

LIZETTE FIGUEROA-RIVERA:

Thank you for the question, Gloria. And Doctor, the next question from the web comes from Dennis. Dennis asks, how does CLL differ from non-Hodgkin lymphoma?

DR. SUSAN O'BRIEN:

Okay, so there are many different types of non-Hodgkin lymphoma, it's a very broad category which just means, as it says, it's not Hodgkin's lymphoma. There is a subset of non-Hodgkin's lymphoma which is essentially CLL without the blood involvement, and that's called SLL, small lymphocytic lymphoma. So in other words, if a patient comes in with an enlarged lymph node, but the blood looks normal, the doctor needs to biopsy that lymph node to find out what's going on. If you look at the lymph node in someone with SLL, it looks like the lymph node of a patient with CLL. However, by definition for it to be CLL, you have to have blood involvement because it's leukemia, right, meaning blood. So the same exact disease basically, if it's only in the lymph nodes without being in the blood, is called SLL. It behaves pretty much the same as CLL. The treatments are the same. So that's why oftentimes when you look up clinical trials, say on clinicaltrials.gov, many trials, the eligibility will be say CLL-slash-SLL. Because small lymphocytic lymphoma is essentially CLL without blood involvement. There are many other types of non-Hodgkin's lymphoma. So we're only talking about a small subset, probably 5% of all lymphomas are SLL. They're more commonly follicular lymphoma or large cell lymphoma.

But it's a good question because sometimes people do get confused. They'll come in and say, well, somebody told me I have lymphoma and somebody told me I have leukemia. Well, if they didn't have any blood involvement at the time it would have been called lymphoma and if they have blood involvement now it would be called leukemia, but it's essentially the disease, SLL or CLL.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. We'll take the next question from the phone audience, please.

OPERATOR:

Thank you. Our next question comes from Rita from Missouri. Please state your question.

RITA:

Thank you, Dr. O'Brien. I have, since we just heard about, I have CLL / SLL. I've had it for 22 years. I was diagnosed in 1994. But in 1999 I was diagnosed with colon cancer. I had a bowel resection, but no treatment. Now I've been on Imbruvica® for two years and I dealt with the diarrhea and everything. I'm doing fine. But it's coming up for my colonoscopy. And I am going to be in a couple of weeks 83 years old. I'm wondering if I still need that colonoscopy. I have had no problems with that, but of course, being on the Imbruvica, periodically I get diarrhea or constipation. One doctor says I'm 83, not to, and the other one says I should have one more. I really don't want – I worry about the prep. Have you had any people that have had colonoscopies and are on Imbruvica?

DR. SUSAN O'BRIEN:

So generally if someone is going to have a colonoscopy because we don't know if there'll be a polyp or something that might need to be biopsied, we do tell people to hold the Imbruvica, which is by the way for people who don't know, ibrutinib. Sorry, I'm used to using the generic names because in academic medicine we don't use product names. But Imbruvica, and I might as well tell you since we're on the topic, that idelalisib, the product name is Zydelig®.

So because of the risk for bleeding with ibrutinib that I talked to you about, and the fact that, say, a patient getting a colonoscopy might have to have a biopsy, we tell people to go off for about seven days before and afterwards.

Now if you've been on the drug for years, going off for seven to fourteen days is not going to hurt anything. You're perfectly safe to do that. So that by itself is not a reason not to have a colonoscopy. Now based on your particular case with your age, etcetera, I think it's something you really need to discuss with your physician because they'll know your other medical problems and things like that and will be able to better advise you on something like that. But in general, good point to make, that if people are going to have any kind of operative procedure Imbruvica needs to be held for seven days before and after the procedure.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And Dillard has another question on ibrutinib or Imbruvica. He says I understand ibrutinib can cause subdural hematomas. Since the symptoms can be nonspecific, should an MRI or CT scan be done periodically if there are a few symptoms, but they're not conclusive?

DR. SUSAN O'BRIEN:

So what we're talking about here is there is a syndrome called subdural hematoma, so a hematoma is nothing but a blood clot, and subdural is outside your brain. So between your skull and your brain you get a blood clot. Most times that people have them, if they're big enough, they do cause symptoms, as you might expect, neurologic symptoms, confusion or weakness or things like that. Rarely they can be asymptomatic. If they're asymptomatic and they're small, we don't do anything about them. In other words slowly the clot gets resorbed over time. They're usually due to trauma, someone bangs their head, but occasionally we do see people, as the person is asking, they're asymptomatic and they're discovered

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by accident for some other reason. But since you don't do anything about them, there's not really any reason to periodically do scans, exposing people to radiation over long periods of time. Because remember you can be on Imbruvica for years. And particularly if it is asymptomatic, the doctor's probably not going to do anything about it. They may consider stopping the drug if they think that that contributed to it, but in terms of actually doing anything to treat the blood clot, no, not if it's asymptomatic. And it's very rare. So given the rarity and the fact that we'd be scanning thousands of people for years and years, it's not really something we would ever do.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And we'll take the next question from the telephone audience, please.

OPERATOR:

Thank you. Our next question comes from Mary from Pennsylvania. Please state your question.

MARY:

Hi, Doctor. I am 55 and have recently been diagnosed with CLL and am asymptomatic. Only thing I have happening to me is constant catching every cold, every infection if I'm around any group of people. Is there anything that I can do, first of all is that normal, and is there anything to keep it from happening? Thank you.

DR. SUSAN O'BRIEN:

Some people with CLL do get an increased number of infections and some don't and it's not always entirely clear why that it is. However, one thing, particularly if the infections are sinus or pulmonary, that your doctor can check, are your gammaglobulin levels. Because in an asymptomatic person who's never been treated, they're less likely to be low, but they can be. In patients who've had a lot of prior treatments, so in other words over time, they're very frequently low. If the IgG, which is a specific type of gammaglobulin is low, and the person's having infections, particularly if they're sinus or pulmonary, we can give them gammaglobulin. It's given intravenously over a couple of hours.

If your gammaglobulin levels are not low, there's really not any other intervention except what you're alluding to, which is trying to minimize places or situations where you would be likely to get an infection. But if this is a problem, you can ask your doctor about checking your gammaglobulin levels.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And we have a question from the web. Donna asks, is iron deficiency a common symptom of CLL? I've had two severe episodes over the past five years. All my other numbers are within the range for someone with CLL.

DR. SUSAN O'BRIEN:

Well, I'm not 100% clear on this, so people with CLL can develop anemia, but it is not iron deficiency, okay? It's as we talked about from kind of the crowding out of the normal red blood cells. Or they can also have something called hemolysis. People with CLL and hemolysis, what happens is their immune system kind of goes haywire and sees their own red blood cell is foreign and starts chewing it up. If that

DR. SUSAN O'BRIEN:

happens people can become anemic and that usually can be treated with prednisone alone and doesn't need treatment of the underlying CLL. So there's all sorts of reasons people can be anemic, but if it's documented iron deficiency, no, that has no relationship to the CLL. The most common cause of iron deficiency in women who are not older is, for example, their periods. So it's not uncommon for women who still get their periods to have some degree of iron deficiency because they're losing blood every month. In an older patient who's iron deficient, that usually prompts an investigation of their GI tract. Because if people are not having their period, they shouldn't be losing blood, and so they shouldn't be having low iron, unless they have just really weird dreadful diet. So that will usually say – if we see somebody who's older and they're developing iron deficiency, they usually need an endoscopy and a colonoscopy because you want to rule out that they're having low level GI blood loss, particularly from, say, an undetected colon cancer or something like that.

So again it depends if it's really iron deficient versus some of the other reasons people with CLL can develop anemia, but no, CLL does not cause iron deficiency anemia.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And we'll take the next question from the telephone audience, please.

OPERATOR:

Thank you. Our next question comes from Jim from Connecticut. Please state your question.

JIM:

At what level would you start treatment? I guess I'm looking for a count. What's the platelet count that would determine, what would the number be that you would determine when treatment would start?

DR. SUSAN O'BRIEN:

So there's not necessarily a fixed number unless it was really low. What we tend to do is look at the trend over time. So there are people, I just mentioned hemolysis, where your immune system is chewing up your red blood cells, you can get similar phenomenon called ITP, which stands for immune thrombocytopenia, which is just a fancy word for low platelets – purpura, which just means bruising.

Some people have low level ITP, but they maintain, say, their platelet count around 90,000. By the way, the normal is over 140 and we don't even really talk about it being low until it's less than 100. But 90,000, most people walk around and they wouldn't have any bleeding problems whatsoever. If it stays at a 90,000 over time, so it's low, but it's very stable low, we generally won't intervene. So there's no fixed number, it's what the trend is over time. If it's 90,000 but then it's 80,000 and then it's 70,000, so it's clearly declining, the first thing the physician has to do is check to figure out if it's ITP, is it where the immune system's chewing up the platelets, or does the patient just have so much disease that the platelets are being crowded out of the bone marrow. The approach would be quite different. If it's the immune problem, where they're chewing up their platelets and they're dropping, just like with the red blood cells, we generally will intervene with either prednisone to inhibit that immune destruction of the red blood cell or platelet, or rituximab, the antibody, can also be used for that purpose. The point is we don't have to go to full blown therapy of the CLL if it's the immune system's that causing it. If it's not the

DR. SUSAN O'BRIEN:

immune system, but the patient just has so much bone marrow disease, then that would call for actual treatment of the underlying CLL to rectify the problem. But again there's no specific number, it's generally the trend that prompts you to treat.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And our next question comes from the web. Jean asks, your opinion on the immunotherapy approach such as CAR-T study in Philadelphia and San Diego?

DR. SUSAN O'BRIEN:

So there are a number of CAR-T trials going on in almost every major city in the United States. The idea behind a CAR-T is you're taking the patient's own T-cells, which are part of their immune system and not part of the leukemia, and they take the T-cells out of the patient, they generate a CAR, which is a chimeric antigen receptor, meaning basically they're putting a protein into the patient's own T-cells, so that when they give the T-cells back they'll attach to the CLL cells and destroy them. So essentially directing or revving up the patient's own immune system. It's a very powerful technique and there have been some people that had more or less failed every therapy and are responding. It's being done in CLL, its being done in acute lymphocytic leukemia, it's being done in lymphoma. Again, there are many trials.

One of the issues with the CAR-Ts is that about 25% of patients will get severe reactions. So as the T-cells are expanding, they can get fever, chills, low blood pressure, wind up in the ICU on a respirator – worst case scenario, not everybody gets it – have to be on blood pressure medication because their blood pressure dropped down so low. Or they can get neurologic side effects like confusion or – and I'm giving you the worst case scenarios here – coma, etcetera.

So one of the problems with CAR-Ts is that they really can only be given in certain centers and the centers have to be very prepared for that, say, 25% of people who will wind up having a severe reaction. On the other hand, can they be very effective? Yes, they can. So I think it's a very exciting technology, which in my mind is still kind of early in development. I certainly wouldn't give a CAR-T as the first therapy for CLL. I think the people who are going on the trials are generally people where they've kind of – you know, the risk is worth it because they are not responding to some of the other agents that we have. And for those people it can be very beneficial. But it's not something I would rush into when we have FCR, when we have ibrutinib, etcetera. It would be reserved for people perhaps who have less options, until I think it becomes an easier technology to administer.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And John asks about long term success or the outlook of stem cell transplants for CLL.

DR. SUSAN O'BRIEN:

We still use stem cell transplants, but my discussion of that would be a little bit like the CAR-T discussion. What I mean by that is if a patient has very high risk disease, we might – and if they're young and fit enough for it, we might recommend a stem cell transplant. Those patients are becoming less frequent because every time a new drug is approved, we have a new option for therapy. So we tend to reserve stem cell transplant not til the patients are on their death beds because you can't do it if they're that sick, but not early on when we have so many good choices for treatments that are easier to give.

DR. SUSAN O'BRIEN:

The problem with stem cell transplant, I talked about the problem with the CARs is, there is risk associated with it. One of the biggest risks is graft-versus-host disease and there are deaths associated with graft-versus-host disease or lots of other problems. Now does everybody get graft-versus-host disease? No. Just like everybody doesn't get the bad side effects with the CARs. But it's a significant enough fraction that again you don't want to take what can be a very good therapy and potentially even curative, and give it to someone, say, newly diagnosed, to give you an extreme, when you've got chemo, you've got FCR, you've got ibrutinib, you've got Zydelig, etcetera.

So in high risk patients, and one would have to know if their prognostic factors are high risk, it's definitely a conversation to have with the doctor. In low risk patients I don't think we're talking about stem cell transplant. In high risk patients who have multiple poor prognostic features, it is a definite consideration if they're fit and able to do it. You don't want to rush into it and do it as the first treatment because there is a risk of death. You also don't want to wait til somebody is, as I said, bed-bound, because you can't do it then. So there's kind of an in between area where it might become a feasible option, but again is generally used for high risk patients where we don't think they'll do as well or their remission will last as long with some of these drugs that we have.

LIZETTE FIGUEROA-RIVERA:

Thank you for that explanation, Doctor. And our next question from Betty is asking about, please talk about what high ZAP-70 means in terms of long term outcomes of therapy.

DR. SUSAN O'BRIEN:

So that's another prognostic factor. We talked about how 17p is high risk and I just was talking about if you're high risk or low risk. There's data ZAP-70 is a protein that's inside the CLL cell. Generally the presence of that protein is a poor prognostic factor. In other words, people, if they're newly diagnosed with ZAP-70, their time to when they require treatment tends to be short and they generally have not done as well with chemotherapy. That may all be changing, though, because so far there's no data, say, with Imbruvica that they do worse. So prognostic factors, people sometimes don't realize this, can actually change with the therapy. In other words, if you have a therapy where 100% of people respond, well, prognostic factors – and we don't – prognostic factors are irrelevant, right? Because everybody's responding. There's no factor to tell you if you're going to respond or not.

So prognostic factors can be specific for a type of therapy, meaning you have this, you may not do well with chemo, like ZAP-70, but so far you may do very well with Imbruvica. So the relevance of some of these factors are changing and I will make one other comment about that. ZAP-70 assays, in other words, the tests to detect it, have not been very reliable. And so most people will often not use ZAP-70, they'll use something that's a much more reliable test, which is called the mutation status. So usually if you're – you'll probably hear nowadays more about mutation status than ZAP-70, partly because the assays for ZAP-70 have been somewhat complicated and not completely reliable.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And the last question today comes from Teresa. She asks, how important is it to see a hematologist-oncologist versus an oncologist?

DR. SUSAN O'BRIEN:

That's an interesting question. So most oncologists in practice don't see much hematology. And the reason for that – unless they have absolutely specialized in it – because most people in private practice, what are the common cancers? colon, lung, breast, prostate – those types of cancer far outnumber leukemias and lymphomas. Far outnumber, okay. So as good as the doctor in the community may be, their experience with leukemias is going to be much less limited than someone in academic medicine who specializes in that area.

So I personally think that if you have a less common cancer like CLL, you should always get a second opinion from somebody who's a specialist, as you refer to a hematologist. Does that mean you have to quit your doctor and not see them anymore? No. What I would do is go to my doctor, my oncologist, if I liked them I'll get their advice, and then I'd go have a second opinion and make sure the specialist agrees with it. And if they do, well, you know your doctor's on the right track and you can keep seeing the doctor that's closer to home that you like. But I do feel strongly that because most people in practice don't have the expertise, just because they don't see the volume of patients that somebody who specializes in rare cancers do.

Believe it or not, every leukemia is essentially a rare cancer. And again to all of you who know plenty of people with CLL, you might not realize that, but again the incidence compared to the incidence in the United States of breast cancer, colon cancer, etcetera, is very, very low. And that's why people in the community generally have not developed the expertise for the rarer cancers because they just don't see as many patients with them. So I think getting a second opinion from somebody who specializes in hematology is always a good idea.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And thank you, everybody for your questions today. Dr. O'Brien, thank you so much for your continued dedication to patients. And for those of you who participated in today's program, we hope the information presented today will assist you and your family in your next steps.

Slide 50. LLS Resources

If we weren't able to get to your question today, please call The Leukemia & Lymphoma Society's Information Specialists at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or reach us by email at infocenter@LLS.org. Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions you may have about support, including financial assistance for treatment.

The Leukemia & Lymphoma Society has a Copay Assistance Program for CLL patients. To find out if you qualify, please call 877-557-2672, where a Copay Specialist will assist you, or you may apply online at www.LLS.org/copay.

Dr. O'Brien, thank you so much for volunteering your time with us today.

On behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Goodbye and we wish you well.

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