

Treating Chronic Lymphocytic Leukemia (CLL): Evaluating and Managing Options

June 11, 2015

Speaker: Rajat Bannerji, MD, PhD



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Slide 1. Welcome & Introductions

OPERATOR:

Hello, everyone, and welcome to a free telephone and web education program, *Treating Chronic Lymphocytic Leukemia (CLL): Evaluating and Managing Options*. It is my pleasure to introduce your moderator Elizabeth Kitlas of The Leukemia & Lymphoma Society (LLS).

ELIZABETH KITLAS:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society, I would like to welcome all of you. Special thanks to Dr. Rajat Bannerji for sharing his time and expertise with us today.

Before we begin, I would like to introduce The Leukemia & Lymphoma Society's Senior Vice President of Research, Dr. Rick Winneker, who will share a few words. Dr. Winneker, please go ahead.

DR. RICK WINNEKER:

Thank you, Liz. 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 a world without blood cancer.

For more than 60 years LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients, and today you will be hearing about some of those new and emerging therapies for patients with CLL.

To date, we have invested over \$1 billion in research to advance therapies and save lives, promising research from bench to bedside.

In addition, as this program demonstrates, we are the leading source of free blood cancer information, education, and support, and we touch patients in their communities through our 61 chapters across the United States and Canada.

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

We are very fortunate to have as our presenter today Dr. Rajat Bannerji, one of the nation's leading experts in chronic lymphocytic leukemia. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. I'd like to thank him for providing us today with important information on CLL.

Thank you all, and now I'll turn the program back to Liz.

ELIZABETH KITLAS:

Thank you, Rick.

We would like to acknowledge and thank Genentech and Biogen, Gilead Sciences Incorporated, and Infinity Pharmaceuticals for support of this program.

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Slide 2. Treating Chronic Lymphocytic Leukemia (CLL): Evaluating and Managing Options

ELIZABETH KITLAS:

I am now pleased to introduce Dr. Rajat Bannerji, Division of Hematologic Malignancies at the Rutgers Cancer Institute of New Jersey, and Associate Professor in the Department of Medicine at the Robert Wood Johnson Medical School in New Brunswick, New Jersey.

I am privileged to turn the program over to you.

Slide 3. Disclosure

DR. RAJAT BANNERJI:

This is Rajat Bannerji. I'm going to go to my disclosure slide before we start the lecture, and I have no disclosures to make regarding any commercial conflicts. I will say that all the data that you'll see in the upcoming slides are from published references and the journal citations should be on the slides. If that's been left out, it was inadvertently left out.

Slide 4. Objectives

I've put up a slide of our objectives for the next 45 minutes to an hour. So we're going to talk about how chronic lymphocytic leukemia is diagnosed; how certain chromosomal changes are used to plan treatment; standard and emerging therapies for chronic lymphocytic leukemia—and as many of you know, the last few years have seen a tremendous amount of research and new medications reaching patients in CLL; a brief discussion of the management of side effects; and finally, just a reminder about the importance of open communication with your healthcare team.

Slide 5. Diagnosis

First we're going to start with the diagnosis of CLL.

Slide 6. CLL

CLL is the most common adult leukemia in the United States. It's a cancer of B-lymphocytes, often abbreviated to B-cells. And these cells can accumulate in the blood, in the bone marrow, in the lymph nodes, in the spleen, or in the liver, most commonly, and more rarely in other organ systems as well.

The incidence of CLL is six individuals per 100,000 and that ends up being about 15,000 new cases of CLL per year being diagnosed in the United States.

It's often discovered nowadays in the setting of a routine or incidental blood count test that you might be getting with your primary care physician. It's a disease of older individuals with the median age of diagnosis at age 70 for men, age 74 for women, but it does have a 2-to-1 preponderance in the men compared to women.

It has a very variable clinical course, and I emphasize that to patients that I meet in the clinic who are newly diagnosed. Approximately a quarter of patients may require therapy at the time of diagnosis, but of the remaining patients half may progress and require therapy at some point, but the other half may have a very slow course of disease and never require therapy.

Slide 7. CLL Cells in a Peripheral Blood Smear

DR. RAJAT BANNERJI:

This is a photomicrograph of a peripheral blood smear. And so this is what a drop of our blood would look like under the microscope on a glass slide. We see a lot of red blood cells in the background, we see some tiny dots, which are the platelets, and then we see four round blue cells and those are CLL lymphocytes. What we don't see here would be a normal lymphocyte to compare these to, but these lymphocytes, the blue part is a little bit more open, less dense or dark than we would see in a normal lymphocyte. So someone looking at the blood smear would recognize these as being abnormal.

Slide 8. Signs and Symptoms of CLL

The signs and symptoms of CLL. So the signs of CLL are things that you would physically feel or see and these include enlarged lymph glands, enlargement of the liver or the spleen, occasionally a rash if the cells involve the skin. And symptoms that patients might feel include profound fatigue, drenching night sweats--and I explain to patients that we all might feel a little sweaty at night on a hot day, but a drenching night sweat, you would be able to literally wring out your pajama t-shirt or your pillow cover because that's how much sweat there would be--unexplained fevers, and unintentional weight loss--and again, significant amount of weight loss, we typically talk about losing 10% of your baseline body weight. So these would be signs and symptoms of CLL.

Slide 9. Diagnosis

Now the diagnosis of CLL. So diagnosis is made with the following characteristics. So we have an elevated white blood cell count where at least 5,000 cells per microliter are described as being the B-cells. The B-cells have certain proteins on their surface and here's a list of them. I won't read out the list to you, but it's kind of like a fingerprint that will allow the pathologist to determine that these particular cells are CLL cells and not some other type of blood cell or blood cancer.

All the CLL cells are clonal--that means they're identical to each other and that's one of the definitions of a cancer. And that clonality can be easily identified by the pathologist, the doctor looking at the lab work, because they express the same protein that we call a light chain, either a Kappa or a Lambda. The normal collection of lymphocytes would have a mixture of both of those proteins, but in a CLL patient all the lymphocytes, they're all copies of each other, they would just have one of those proteins.

Another characteristic is that patients have fewer than 55% of their cells being described as something called a prolymphocyte. And these are even larger, more aggressive-looking lymphocytes and the disease has a more aggressive course and is treated somewhat differently.

So those four features that we just talked about would help with the diagnosis of CLL. If you look at those features, basically we can get that information just from the patient's blood. So to make a diagnosis of CLL, we typically do not need to do a bone marrow biopsy and we typically do not need to do any kind of surgical or needle biopsy of a lymph gland. Occasionally, though, we'll have patients who have enlarged lymph nodes or an enlarged liver or spleen, but we don't see any of these cells in the blood. So those patients would get a biopsy of the lymph node and we would find similar cells to those I described just now in the lymph node. And that disease is given a name of small lymphocytic lymphoma, SLL. But when we approach a patient in regards to treatment, we do treat CLL and SLL identically.

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Now there's a new, relatively new, idea, as our technology has gotten more sophisticated in finding these cells in the blood, and that is that if we see a small population of these cells in the blood without any of the signs or symptoms of CLL that I talked about in the previous slide, and the population—we have a numeric cutoff, it's less than 5,000 of these cells per microliter of blood—we don't give the patient a diagnosis of leukemia, we call this condition monoclonal B-lymphocytosis or MBL for short. And they're in the bullets here, what we can find is that these small populations of CLL-like cells are seen in about 5% of just completely healthy individuals over age 40, and as patients get older, the percentage of healthy people with these cells increases. So in fact, healthy individuals in their 80s, some studies have shown that almost a quarter of these individuals would have these CLL-like cells in a small population that we can detect with a test called flow cytometry. But of course, a quarter of 80 year olds don't have CLL, so this MBL is kind of a precursor and some people then go on to develop CLL.

Slide 10. A Model of How CLL May Develop in an Individual

In this next cartoon, and I'll try to walk through this, gives an idea of how that might happen. So if you go to the left side of the slide you'll see just a single cell called the HSC or hematopoietic stem cell, and that's kind of like the parental cell that's going to give rise to all the cells of your blood system. There's a little lightning bolt, so that cell has a mutation occurring in it and that gives rise to a cell that might be a precursor for CLL. And then you have a burst of new cells being born; as we're going across the middle of the slide, you see that one cell has now gone to many cells. And what's happening is that that CLL cell is reacting to proteins and those proteins are stimulating it to divide and there are more and more cells happening. And this is where we might get these small populations that are called MBL or monoclonal B-lymphocytes. So they're like CLL, but not quite there.

And then you see these, towards the right hand of the slide, the double lightning bolt. So that means that some population has acquired additional mutations that make those cells kind of cross the line to become a true cancer and become CLL.

And so as we get older, we all—sorry, not all of us, but many of us will have cells in that middle part of the slide, the MBL cells, in our blood, but not all of us end up with the mutations that lead to CLL or not all the patients who have those precursor cells.

This cartoon, though, does emphasize one point and that is we feel that almost everyone with CLL, and there's some data to support that, likely had a preexisting pre-CLL population that then progressed.

Slide 11. What Else Could It Be?

Now what else could it be? So when you might have a blood count done, it has an elevated white blood cell count, the doctor says that most of the white blood cells are lymphocytes, does that automatically mean that it's going to be CLL? It does not. Most often it is CLL, but there are other diseases with small lymphocytes in the blood and the oncologist and the pathologist need to be sure that the diagnosis is CLL and not one of these other diseases.

And so here's just kind of a list of things that we consider or look at. A disease called mantle cell lymphoma; a disease called hairy cell leukemia; splenic marginal zone lymphoma; follicular lymphoma; MALT lymphoma, that's sometimes also called nodal marginal zone lymphoma; lymphoplasmacytic

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lymphoma, that's sometimes called Waldenström's macroglobulinemia; and that more aggressive version called prolymphocytic leukemia. So again, the doctor should be sure with the testing that they do that it is not one of these other possibilities.

Slide 12. Chromosome Changes and Implications for Treatment

If a diagnosis of CLL has been made, the next important part is to look at the genetics of the CLL cell because it does have some implications for prognosis and treatment. And so this next section will be on chromosome changes and implications for treatment.

Now here we're going to talk about common chromosomal changes in CLL. And I'll just pause for a second to explain that.

The chromosomes are long strands of DNA wrapped around proteins, and all of the information in our bodies that builds us as individuals is in our DNA. So using the computer analogy, that's kind of the software for our body.

The chromosomes are packaged and paired and they're numbered. And what we see in CLL is sometimes that we have large breaks in the chromosomes that can be detected, or even switching around of the chromosomes, where part of one chromosome is broken off and switched with a part of another chromosome and then kind of glued back on to the wrong chromosome. So once the diagnosis is made, there are some common tests that are done to look for some repeated changes or common changes that occur in CLL.

Slide 13. Common Chromosome Changes in CLL

I'm going to go through the most common changes that we look for and then I'll show you a picture slide that will give a more visual representation of how this is looked at.

The test that's used most commonly is a test called FISH or fluorescence in situ hybridization. And the next slide will show us how the FISH test works, but suffice it to say that what they're going to look for is they're going to look for a breakage of the long arm of chromosome 13. We call that deletion of 13q. And we know that patients who have this, surprisingly, actually do better than patients without any abnormality in their chromosomes. So often when we think of a mutation, we think that that's a bad thing. In this case the loss of this part of chromosome 13 actually leads to a more benign form of CLL.

We can have extra copies of chromosomes, so the next one, trisomy chromosome 12. And then we can have some other breakpoints, deletion of chromosome 11q or loss of chromosome 17p. And the two that are on the bottom of the screen are typically associated with a worse prognosis, a more aggressive form of CLL. And people have thought about why that might be and some of the hypotheses are related to genes that might be in those parts of the chromosome that are lost. And so in chromosome 11, people think that the main reason that that's bad is because you lose a gene called ataxia-telangiectasia, and that gene is important in causing the cell to stop dividing and to fix any mistakes in the DNA. And so a cancer cell doesn't want that, it doesn't want its mistakes to be fixed because those mistakes are what allow it to grow fast and be a cancer cell.

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The other bad prognostic marker, and in fact the worst prognostic marker, is loss of the short arm of chromosome 17. We call that deletion 17p. And that loses a very important gene called P53. And P53 is kind of a master gene that regulates DNA repair. And again, for a cancer cell, fixing the mistake is a bad thing. And so loss of chromosome 17p allows for a more aggressive type of CLL.

Slide 14. Genomic Aberrations Are Frequently Detected by FISH in CLL-like MBL Clones

Now this picture is a picture of the FISH test that the lab is doing to let us know if any of those chromosome changes have occurred. So I'll walk you through the picture. And what we're looking at is we're looking at, in the blue circles, are individual cells being looked at under a microscope. And the cells have been treated with what we call probes, so these are going to be little bits of DNA or RNA that will bind to certain chromosomes and each of them will be tagged with a chemical that gives off a certain color light.

And so I think we'll ignore panel A for a moment. But if you look at panel B, you can see, if we look at the top blue circle, which is an individual cell nucleus, that there are three green dots and two red dots. And if you look at the bottom cell, there are also three green dots there and two red dots. That would be a patient with trisomy 12 because the lab, before they've done this, have known that they're using a probe, something that's going to bind to chromosome 12 and give off a green light. And they would expect normally only two copies of chromosome 12 and two green dots, but now we see three green dots, and this is how they would diagnose that this particular patient had trisomy 12.

If we look at panel C, we can clearly see that both of the cells have one red dot and two green dots. Now the color doesn't matter because the lab can have any particular color attached to the probes. In this particular case that's a picture of someone with deletion of chromosome 17, so the marker that would bind to chromosome 17p was set up to give off a red color on the microscope, and we should normally see two of those. And because we only see one, we can tell that this patient is missing one of their chromosome 17s, and the probe is specifically made to bind to the short arm of the chromosome, what we call the P arm, and so this is deletion 17p. And this is how the patient would be diagnosed to have that particular chromosomal abnormality.

And I only go through this in a little bit of detail because everyone that's diagnosed with CLL should have a FISH test done on their blood to understand which of these particular mutations they have. And this is just a way for you to have a visualization of how that information was actually acquired.

Slide 15. Clinical Implications of Chromosome Changes

And so why get all this information? Well, there are some very important clinical implications of the chromosomal changes. And we'll just go through these.

The first one is that the time from diagnosis of CLL to actually needing treatment of CLL varies according to the chromosomal changes found in a patient's CLL cell. And in the next slide that we'll get to, we'll see how much that variance can be affected by the different mutations.

Next, the average survival of patients can vary according to the chromosomal changes. And so the higher risk chromosomal changes may predict for shorter survival. How well various treatments work in controlling the CLL can also vary according to the chromosomal changes. And some treatments such as

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a drug called alemtuzumab, or Campath®, or the use of bone marrow transplantation work equally well regardless of the chromosome change that's found. And that's important because not all treatments work across all the chromosome changes that we might see.

Now can a patient have more than one abnormality at the same time? They absolutely can. And the way we then talk about that patient's risk is we look at the quote-unquote, the worst of the abnormalities they have and that is how we approach the patient.

To just have a simple example of that, the highest risk chromosome change would be loss of chromosome 17p. If that same person also had trisomy 12, which is kind of intermediate or even good, it wouldn't matter, the behavior of their disease would still follow the behavior of 17p. So it would be the worst of the two abnormalities would drive the behavior of the CLL.

Slide 16. Time to First Treatment by FISH Results

We're looking at a somewhat complicated graph, and what this graph is looking at is the time from diagnosis to when a patient first needs treatment, based on the results of the FISH test. And what I would just point out to you is that there's a kind of a blue line at one side of the graph and there is a yellow line and a black line at the other side of the graph. The blue line is deletion chromosome 17p, that's the most aggressive of the types of CLL based on these chromosomal changes. And as you can see, the blue line trends downward very quickly, and so if we look we would say about half the patients would need to be treated within kind of a year and a half of being diagnosed, at least on this particular graph. Whereas the yellow and black lines go down at a very shallow grade and half of those patients may not require treatment in a number of years. And so this type of graph, called the Kaplan-Meier curve, helps us look at the data and determine how aggressive or not a particular patient's CLL would be.

Slide 17. Impact of Molecular Markers on Prognosis in Chronic Lymphocytic Leukemia

And in I think a more self-explanatory form, the next slide looks at this information in the form of a graph—in the form of a table, excuse me. And I think we'll go over the numbers in the table in the section that says "Cytogenetics," the top of the table. And those are the FISH results that we would typically expect after the FISH test is done.

And so if we look, the top is deletion 13p. That's the one where patients actually do better than not having any mutation at all. And as you can see, 55% of patients will have this abnormality when they're diagnosed—over half. Their time to requiring treatment, that's the TTT in months—time to treatment—is 92 months, so many, many years without requiring treatment, and their overall survival on average is 133 months.

A patient with a normal FISH result, meaning they don't have any of the abnormalities, we see that in about 18% of patients. And their average time to treatment is 49 months and survival average is 111 months. And as we go down to the more aggressive ones, we'll see—if we go to the most aggressive, deletion 17p—we only see that in about 9% of newly diagnosed patients with CLL. But their average time to treatment is relatively short. Instead of years and years it's less than a year, about 9 months on average, and overall survival is relatively short, only about 32 months on average. So even less than 3 years.

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Now the caveat to these numbers is if you look at the reference—that was a study published in the year 2000. And we know that the treatment of CLL has changed dramatically from the year 2000 to now in 2015. So I wouldn't have anyone fixate on these particular numbers. But it's still true that even in the era of these new treatments, that the deletion 17p carrying CLL, is the most aggressive form and does do a little bit worse than the other abnormalities—significantly worse than the other chromosomal abnormalities—and we'll see that when we go to the treatment section and look at information with some of the new therapies that are available.

Slide 18. Some Treatments Work Less Well With High-Risk Chromosome Changes

We've moved on to a slide where we're looking at a very common chemotherapy regimen used in the treatment of CLL called bendamustine, a chemotherapy drug, and rituximab, a monoclonal antibody. And people may know the drug bendamustine by the trade name Treanda® and may have heard their doctor talk about a regimen that they call BR, just the abbreviation.

And what we're looking at here is a table that looks at bendamustine-Rituxan® being used in the treatment of patients for the first time as their first treatment for CLL, that's first-line, or in patients who've had some other treatment and the CLL has come back and now they're getting the bendamustine-Rituxan and that's the column labeled "Relapsed."

And the point I want to make here, and I'll just do it for the first-line, but the data, you can look at later on your own, shows that in the first-line setting, bendamustine-Rituxan in this particular study had an 88% response rate with 23% of the patients having a complete response and the progression-free survival—and that's a term that you'll hear me using a lot when we talk about treatment; progression-free survival just means the period of time from when they started a particular treatment until the disease started growing again. So in this particular study for bendamustine-Rituxan, the progression-free survival was about 34 months, almost 3 years, on average.

Now if you still go down that line, you'll see patients with deletion 17p had significantly inferior outcomes. So they did much worse than the general population of patients. So instead of 88% of the patients responding to this treatment of the deletion 17p, only about 37% responded and none of them had a complete response, meaning that all the CLL went away. And the period of time following treatment before the CLL started to grow again, instead of 3 years was only about 8 months. So we know that the deletion 17p population has a much more aggressive disease and that even treatments that are very active, such as bendamustine-Rituxan, do not work as well in that high-risk population.

Slide 19. IgVH Somatic Hypermutation

Here I'm just going to mention a test that you might hear about at the doctor's office regarding CLL, and this is another test for prognosticating CLL. And that's called the immunoglobulin variable chain—variable region of the heavy chain, or IgVH for short. And the mutational status of the IgVH.

The only thing to remember here is that if you have an unmutated IgVH, that's actually felt to be a more aggressive type of CLL. And if you have a mutated IgVH, that's supposed to predict for a less aggressive type of CLL. And we have a number of these prognostic systems right now. We don't routinely base particular treatment on the IgVH status, but it may become important. For example, there are some early

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data showing that the drug ibrutinib behaves differently based on the patient's IgVH status of their CLL cells. So I don't want to go further into that right now, but I just have this slide here to let you know that there are other things that we look at in prognosis.

Slide 20. Prognostic Markers and Treatment Decisions

And so this is a bit of a summary slide here: prognostic markers and treatment decisions. As CLL biology is discovered, new prognostic and predictive markers have been proposed. Currently—so this is the important part—there's no data to support us using a particular therapy with a particular risk population, with the exception—and this is the last bullet—of deletion 17p.

So there are some ongoing studies and I listed them, two of them at least, that talk about, for example, patients with some form of high-risk disease. Should they be treated at diagnosis or only if they're symptomatic? Should we alter treatment based on their genetic changes? But those studies are ongoing.

Currently if you have any of those changes that we looked at in the previous slides—so that includes deletion of chromosome 13, an extra copy or trisomy of chromosome 12, deletion of chromosome 11, deletion of chromosome 17—the only one of those test results that we would actually base our treatment on is the loss of chromosome 17p, since that's a very aggressive and poor risk abnormality.

Slide 21. Observed OS in Patients from the training series compared with the expected OS in the matched general population

This is a very complicated slide. We're not going to go through it in any detail at all, except to look at the top of the slide where you see the various short colored lines and an explanation of what they are.

If you look at the panel A and you look at the colored lines, those are the mutations that we would see—the chromosomal abnormalities, excuse me—that we would see using the FISH testing: so deletion 13q, normal, plus 12, means trisomy 12 or a third copy of chromosome 12, deletion 11q and deletion 17p. And that's what we've been talking about for the last 10 minutes or so.

If you look to the right, you'll see those same changes, but then you see some other things added in there. And what people are looking at now is incorporating certain genetic mutations as well as the chromosomal changes. So there are some mutations that may predict for a more aggressive CLL, such as mutations in a gene called NOTCH or a gene called SF3B1 or in a gene called BIRC3. And all this means is that in the future we may be getting more and more information to help guide us in terms of prognosis and perhaps even treatment of patients with CLL.

And one analogy I use with patients regarding chromosomes and genes is, if you think of a tall skyscraper or apartment building, that would be a chromosome, and if you think of a gene, that would be a single apartment in the building. So when we look at these chromosomal abnormalities with the FISH testing, we're looking at essentially knocking down half the building. That's how big a change that is. When we look at some of these mutations, we're looking at a broken door in one apartment, to use that analogy. But what we find is some of the genes are very important, and so in the future people will be getting more information not just on the chromosomes but on certain important individual genes and we'll be incorporating that into the prognosis of CLL and perhaps someday even in the treatment of CLL.

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Slide 22. A Partial List of NCCN Recommendations for del17p CLL

DR. RAJAT BANNERJI:

Now a pause here, before we get into the formal section on treatment in this lecture, just a list of recommendations from the NCCN [National Comprehensive Cancer Network], which is a group of leading cancer centers in the US on what to do with deletion 17p CLL or the highest risk CLL. And what they recommend in patients who are newly diagnosed is that the first option should always be an appropriate clinical trial. And that is because this is a very high-risk disease and looking at novel therapies that may be active in that disease is really a very important goal. And in fact, therapeutically can be quite important. We'll talk about some drugs that seem to be active in that setting.

Then if there is no clinical trial available, ibrutinib, an oral agent which we'll talk about a little bit more as we go forward, is an important option and may be the go-to drug now for many patients with deletion 17p CLL if they can't have access to a clinical trial. And then there are other options that include rituximab with steroids; a drug called alemtuzumab, or Campath, with steroids; and then various chemotherapy regimens.

And then at the bottom is just a partial list for patients who have relapsed disease with deletion 17p and just some of the options that are available among many, but they include ibrutinib again, another oral drug called idelalisib, another oral drug called lenalidomide, and an antibody called ofatumumab. And, as I say, there would be other choices as well.

Slide 23. Treatment

Now we're going to talk about treatment.

Slide 24. Indications for Treatment

The indications for treatment. An important point here is that having the diagnosis of CLL in and of itself is not a reason to undergo treatment. And we say that because almost all of our treatments for CLL can control the disease, but other than bone marrow transplant, none of them are curative. They don't cure the disease. And so if someone's feeling perfectly well, they're having no symptoms from the CLL, it's just an abnormality with a high white count that they see on a routine blood test but they otherwise feel fine, then if we treat them all we're going to do is cause the patient to have side effects from our chemotherapy or our targeted therapy, whatever treatment we use, but we're not going to make them feel any better. And at least right now, since we can't cure them, there doesn't seem to be a reason to jump to treatment right away.

However, if the patient starts having any of the things described on this slide, then we should consider treatment. And these include symptoms such as weight loss, fatigue, fever or night sweats that we talked about before, or effects on the bone marrow—so significant anemia, a drop in the red blood cells, or thrombocytopenia, a drop in the platelets. Those are the little cell fragments that help our body to clot if we get a cut or a nick. So if those cells that are also made in the bone marrow, the normal cells, start falling, that's a reason to treat the CLL.

If patients have—and I'm sorry I used these abbreviations—autoimmune hemolytic anemia (AIHA) or immune thrombocytopenia (ITP) that are poorly responsive to steroids, then we should treat the CLL. And what these two problems are are abnormalities of our immune system caused by the CLL that causes our

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own body's immune system to attack our red blood cells or our platelets. If that complication occurs and it can't be stopped with just taking prednisone tablets, for example, then that would be a reason to actually treat the CLL.

If there are very large lymph nodes or a large spleen that's physically uncomfortable, that would be a reason to treat the CLL. Or a very fast doubling time—so here we say less than 6 months. So one day the white blood cell count is 25,000 and then 4 months later it's 50,000, so it's doubling very quickly. That might be a reason to treat the CLL.

Now the last point is important. If all that's going on is kind of an increase in the blood count and no other symptoms, then there is no magic number or threshold number that we say is the number that you need to treat at. And so there may be patients with blood counts well above 100,000 who feel perfectly fine, and they would still be watched and be left alone.

Slide 25. Evolution of CLL 1st-line Treatment

Now I'm going to go through the next few slides relatively quickly. This is just a bit of a history lesson, so I don't need to linger here. But this is the evolution of treatment for CLL as initial treatment. Years ago there was an oral—and still is—an oral chemotherapy drug called chlorambucil, but that used to be the only therapy for CLL. In the 1980s a very potent purine analog chemotherapy drug called fludarabine came into use and related drugs to fludarabine like pentostatin. Then clinical trials looked at combining fludarabine with other chemotherapy drugs in patients, like the alkylating drug cyclophosphamide.

Slide 26. FCR (Fludarabine, Cyclophosphamide, Rituxan)

And then a very important advance was the addition to those two agents of the monoclonal antibody drug rituximab or Rituxan for short. And as we added to that backbone, the activity against CLL increased significantly. But the important point was with the addition of Rituxan to the chemotherapy that we first started seeing an improvement in survival of patients with CLL due to treatment. So even though the CLL was not necessarily being cured, the patients who were treated with the FCR regimen were actually living longer than patients who might have been treated with just chemotherapy alone without the Rituxan or treated with chlorambucil or just supportive care.

There are numbers in the slides regarding response rates and survival advantage or time to progression, and you can look at those on your own. One point that I will say is there's some very intriguing data which is not on the slide, from the MD Anderson Cancer Center, looking at their patients that have been treated with this regimen, fludarabine-cyclophosphamide-Rituxan, and what they find is that patients who have the IgHV-mutated—remember we talked about that test in that one slide—with one of the good risk abnormalities on the FISH, either deletion 13q or trisomy 12, that some of those patients seemed to respond to the FCR regimen, and if we look at them over time, they are not relapsing. So there may be a subset of patients who it's too early to say that they're cured, but are certainly having a very long disease-free period with FCR. And so again that would be patients whose CLL are the IgHV-mutated with either deletion 13q or trisomy 12.

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Slide 27. Survival of Patients receiving F, FC/M, and FCR as initial therapy of CLL at the MD Anderson Cancer Center

DR. RAJAT BANNERJI:

Now this is an important slide, just showing progress in treatment. So there are three lines on this slide, and this is data, again, from the MD Anderson Cancer Center, and this is looking at how CLL treatment has changed over time. And the lines are survival in years. And so the lowest line is the drug fludarabine by itself, the middle line is fludarabine combined with cyclophosphamide, and then the big jump is fludarabine combined with cyclophosphamide and Rituxan.

And what you can see is the upper left corner of that graph says 1.0 and that means 100% of the patients. And in the bottom we're looking at time in months, but we're really going out a number of years. You can see the graph goes out to 108 months. And the top line shows that more people are surviving longer with the FCR regimen than with previous chemotherapy combinations, and that's showing that over time the evolution of treatment of CLL has resulted in better survival of patients. And it would be very interesting in a few years to see this graph with some additional lines plotted looking at our new therapies, our oral therapies, for CLL and the progress that's being made with those.

Slide 28. B-cell Receptor (BCR)

The next thing we're going to talk about is a protein on the surface of the CLL cell called the B-cell receptor. And it's important to know about the B-cell receptor because a lot of the transformative treatments available for CLL now are based on inhibiting the signal from the B-cell receptor.

One way you can think about the B-cell receptor is that it's a switch on the surface of the B-cell, the CLL cell, and if you flip that switch you're going to send a signal to the cell causing it to divide, to want to survive longer, so like any cancer cell, live for a very long time and to make more and more of itself. So to treat the disease we want to turn that switch off.

Slide 29. Antigen-dependent B-cell Receptor (BCR) Signaling and its targeting by small-molecule inhibitors

If we look at the next slide, it's kind of a cartoon, and on the left of the cartoon you'll see these blue Y-shaped diagram and that's just a cartoon representation of the B-cell receptor. The little brown boxes, antigen, those are proteins that the B-cell receptor is seeing that acts to flip the switch on. And if you look at kind of the jellybeans or circles below those blue Ys, to get that signal from the outside of the cell to the cell nucleus, to turn the cell's DNA on and cause it to make more copies of the cell, it's not a straight shot. There are a lot of intervening switches or proteins along the way and that's what all of those circles are, and each of them have been named with some abbreviations. And there are actually drugs that hit some of those important intermediary steps. And so you can see a blue jellybean that says BTK for Bruton's tyrosine kinase, and that's inhibited by the drug ibrutinib. You can see kind of a gray circle that says PI3K with the Greek letter Delta and it has a GS-1101 under it; well, that's idelalisib and it's a PI3 kinase inhibitor that can stop the pathway. And then there's a target called SYK with a drug called fostamatinib which is actually not in development any more for CLL, but another potential target to stop the growth signal for CLL cells.

Slide 30. Ibrutinib

DR. RAJAT BANNERJI:

This is ibrutinib. It's an oral drug. There was a recent large clinical study comparing it to one of the antibodies called ofatumumab, and the study showed that patients who were treated with ibrutinib, their disease did not progress for an extended period of time. And if we looked at the number of patients who were alive with CLL at 1 year from the start of treatment, 90% who got the ibrutinib drug were alive compared to only about 81% who got the control drug ofatumumab. And importantly—and it's one of the lower bullets on this slide—the results in response were very similar to patients who had the bad risk deletion 17p compared to patients who didn't. And based on this, the FDA-approved ibrutinib for initial treatment for patients with deletion 17p and second-line treatment for anyone with CLL.

Slide 31. Progression-free and Overall Survival

Here we have a graph again and the graph, the top of the graph is looking at ibrutinib and the control drug ofatumumab. The one where the lines separate a lot is looking at progression-free survival, so many more of the ibrutinib patients go on for a longer time without their CLL progressing. And then the bottom half of the graph shows again two lines, still separated, but a little bit closer apart, and that's survival, that's people being alive, and again, though, more people treated with ibrutinib survived out to the end of that time period, that they were being followed, compared to people treated with the control drug.

Slide 32. Idelalisib

Another oral drug that's now available is a drug called idelalisib that goes after that other target that we saw in the cartoon called PI3 kinase Delta.

And we'll look at kind of a cartoon of a clinical study with the idelalisib shortly as well, but the important point is that idelalisib also was active in patients with deletion 17p, as active as it was in all other patients with CLL.

The important point in that study is that idelalisib was combined with the drug Rituxan and when it was approved by the FDA, it was approved as a combination.

Slide 33. Subgroup Analysis of High-Risk Groups

And so this is a cartoon of the design of the study that led to the approval of this drug idelalisib. You can see a red arrow and that is placebo or quote-unquote a sugar pill, combined with rituximab, compared to the blue arrow, which is idelalisib plus rituximab. Now the interesting thing on this study was that if patients progressed, then they were allowed to either increase their dose of idelalisib if they were actually on that before, or if they were on the dummy pill they were allowed to cross over and get idelalisib. So everyone eventually got the study drug.

Slide 34. Change in Lymph Node Size

And this is what we call a waterfall plot. And what it is is a summary: each line is an individual patient, and you see a zero mark. If the lines are below the zero that means the individual patient's tumors shrank and you can see some percentages. People at 100% shrinkage of their tumor, that means it all went away and then so on. And in the idelalisib-rituximab group, every single patient had tumor

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shrinkage. Some had maybe more modest tumor shrinkage than others, but every single patient had shrinkage of any lymph nodes that were involved with the CLL. Whereas in the group with rituximab and placebo, some patients had shrinkage and some patients actually had, despite treatment, had growth of their CLL.

Slide 35. Progression-free and Overall Survival

And this is again a very similar type of graph to the one that we showed with the ibrutinib, showing in the blue line the idelalisib, and if you look at the bottom half of the graph, again a survival advantage of idelalisib combined with Rituxan versus Rituxan alone essentially.

Now we're getting a little short on time, so I'm going to go through a number of treatments and we'll talk about with all of these treatments available, how do we manage the sequence of treatments that we might use in a patient?

Slide 36. Anti-CD20 Monoclonal Antibodies to Treat CLL

An important category of drugs that I'm going to go over now are the anti-CD20 monoclonal antibodies. And these are proteins that are kind of like smart bombs. They target this protein CD20 that's on the surface of the CLL cells and they hone right into the cells and kill them.

The first one that was approved and has been used now for many years is a drug called rituximab. And then there have been other versions that seem to be more and more potent, ofatumumab and now more recently obinutuzumab. And you may have heard of ofatumumab by the trade name Arzerra® and obinutuzumab by the trade name Gazyva®.

Slide 37. Response Rates and Progression-free Survival With Obinutuzumab–Chlorambucil or Rituximab–Chlorambucil versus Chlorambucil Alone

There was a study done that compared patients who were being treated for the first time with either chlorambucil—that's an oral chemotherapy agent—or a combination of chlorambucil and rituximab or a combination of chlorambucil and obinutuzumab. And if you just look at the top part of this figure where you see the vertical lines, the vertical bars, there's a purple bar, a green bar, and a blue bar. The green bar is the chemotherapy agent chlorambucil as a pill. The purple bar is obinutuzumab, and as you can see, it's taller than any of the other two bars, meaning more patients responded. And if you look, the obinutuzumab has more patients in the light purple than the other graphs do in their lighter shades. And those are patients that had a complete response, so all evidence of the CLL went away. And so in this very nice three-arm study you can see that both Rituxan and obinutuzumab had responses in CLL in combination with chlorambucil, and both were better than chlorambucil alone, but the obinutuzumab and chlorambucil combination was actually better than the rituximab-chlorambucil combination.

And this data allows—first of all, it allowed obinutuzumab to get FDA approval in combination with chlorambucil, but it makes it a very reasonable choice, for patients who might not tolerate chemotherapy as an active treatment for their CLL, as their first treatment for CLL.

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Slide 38. Response Rates and Progression-free Survival With Obinutuzumab–Chlorambucil versus Rituximab–Chlorambucil

DR. RAJAT BANNERJI:

And the second picture, very similar to the first, is a direct comparison of obinutuzumab to the Rituxan combination and also the number of patients who had a complete response.

Slide 39. Allogeneic Hematopoietic Stem Cell Transplant

We talked about chemotherapy. We talked about oral therapies: ibrutinib and idelalisib. And we talked about antibody therapies: rituximab, ofatumumab, and obinutuzumab. So there are a number of choices, and so how do we go about treating patients?

I think it's still legitimate to treat a healthy younger patient with CLL with the most aggressive chemotherapy regimen, and that's the three drug combination of fludarabine, cyclophosphamide, rituximab. Maybe older fit patients with a two-drug regimen of bendamustine and rituximab. Maybe an older patient who may not tolerate chemotherapy that well with chlorambucil and an antibody such as obinutuzumab. But the only curative therapy for CLL is bone marrow transplant, and we haven't talked about that, so we're going to touch on that right now.

One of the things we know about bone marrow transplant in CLL is that its success is equal whether or not they have those high-risk genetic changes, and that transplant may actually cure some people of CLL, meaning the CLL never comes back.

Unfortunately transplant is only possible in a small minority of CLL patients and that is because the recipients have to be healthy, they have to be of a slightly younger age so that a bone marrow transplant is possible, and they have a good donor. Even with modern transplant techniques, there is a risk of death due to complications of transplant that's pretty significant: 15 to 30% over the first 2 years following transplant. And almost a quarter of patients with longstanding graft-versus-host disease, which is a complication of transplant where the donor immune system is actually going after normal organs of the patient, of the recipient. And so they can have damage to their gastrointestinal system, to their lungs, to their liver, to their skin. And it can be very debilitating. So these toxicities have to be taken into account.

Long-term survival rates have been shown, up to 45 to 60%, in various studies in CLL patients with transplant. And so in patients who might have the high-risk features of CLL, that's actually—those are very good results, and so transplant is still very much a valid option for properly selected patients.

Slide 40. When to transplant in high-risk CLL

And so when might we think of transplanting in CLL? We would think of transplanting high-risk patients, defined as patients who are refractory to drugs like fludarabine, meaning that the CLL came back in a short period of time, especially to combinations of fludarabine with Rituxan, or that fludarabine didn't work at all. And, of course, patients with the deletion 17p that we've been talking about all along or a mutation in a very important gene that's in that part of the DNA called P53.

Below I have some of the recommendations from a large society of bone marrow transplant in Europe called the EBMT [European Society for Blood and Marrow Transplantation]. And what they recommend for CLL is transplant after you've treated a patient on either a clinical trial or one of the new treatments,

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and consider transplant if that initial treatment does not work. And they even say, well, maybe consider transplant if the initial treatment does work because we don't have really long, long follow-up with any of the newer oral therapies.

With ibrutinib there's a recent publication that looked at 3 years of continuous ibrutinib therapy and that's probably the longest follow-up we have so far. But of course, the data will change as time goes on.

And certainly consider transplant in patients with high-risk CLL as defined above, who are young, healthy, and have a perfectly matched donor, so they would have the best odds with a transplant and that would be reasonable for them.

Slide 41. Emerging Therapies

Okay, emerging therapies. And I'm going to go through this, and this is quite important. And we are getting towards the end of the talk, so we should have reasonable bit of time for questions.

Slide 42. Important Clinical Trails Currently Underway

Alright, so before we got to transplant I gave you a summary of how we would approach a patient now, but the question is going forward with these new oral drugs, can they replace chemotherapy as the first treatment for a patient? And there are some very important clinical trials going on right now that will help us answer those questions.

In the US there's a trial called the ECOG 1912 that's looking at younger patients, defined as age 18 to 70, and that's looking at people—half the people getting the FCR three drug chemotherapy regimen we've already talked about or the other half of the patients on the study getting ibrutinib, the oral drug, plus Rituxan. And as you can see, there's a similar trial going on in Europe, and that we don't expect results from these trials for another 2 or 3 years.

In older patients we have a very important trial, again looking at the standard chemotherapy for older patients, bendamustine-Rituxan being compared to ibrutinib alone or to ibrutinib plus rituximab. And on this particular trial if a patient enrolls, they can be randomized to one of those three groups.

A question that we didn't talk about and that's not defined as being standard but is being looked at in clinical trials is the idea of maintenance. Which means that we've gotten you into complete remission, can we put you on a well-tolerated drug for a long period of time that keeps you in, or maintains, that remission? And so there are two maintenance trials going on. One in Europe through the German Study Group and one in the US through the company Celgene looking at maintenance with a drug, a pill, called lenalidomide following treatment.

And can we combine these new pills, like ibrutinib, with chemotherapy to make things work even better? And there was, just a few weeks ago, information presented at the American Society of Clinical Oncology (ASCO) meeting where they showed that the bendamustine-Rituxan chemotherapy when combined with ibrutinib was much more active than the chemotherapy without the ibrutinib.

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Slide 43. Treatments in development

DR. RAJAT BANNERJI:

And I want to touch on some drugs in development that are very important. I think one of the most exciting is this drug called venetoclax, ABT-199. It's a pill, it's an oral therapy; it seems to be very active in the high-risk deletion 17p. And our site has been one of the centers on this study, and at least in my experience with the handful of patients we've treated seems to be very well tolerated. We'll have to see, of course, what the full clinical study's data shows, but that is one that again hopefully the company will be taking to the FDA in the next few years and would give us another excellent option.

And then another PI3 kinase inhibitor from a different company, called IPI-145 or duvelisib, and that's also in late-stage trials and may be coming out in a few years.

Slide 44. Chimeric Antigen Receptor Modified T Cells (CAR-T) therapy of CLL

Some people, and I'll take 30 seconds to touch on this, may have heard of a therapy called CAR-T therapy, and this got a lot of press recently. And that is where the doctors take out the T-lymphocytes from a patient; then in the lab they modify those T-cells, which is a type of immune cell, to attack the CLL cell. Then they give the T-cells back to the patient, and the T-cells go after the patient's CLL. Now the data is in just handfuls of patients; the initial study from the University of Pennsylvania was only about 10 patients, and they recently showed some very preliminary data in a slightly bigger study with 30 patients, but it does seem to be active and may represent an option for some very carefully selected patients.

Now this type of treatment does have some unique toxicities, including a thing called a cytokine release syndrome, where kind of the entire immune system is turned on and patients can have very severe side effects in terms of fluid getting into the lungs, flu-like symptoms, problems with their blood pressure, etc. So although the CAR-T therapy sounds very exciting, it is not without its own risks.

Slide 45. Toxicities of Treatment

Now the next section is toxicities of treatment. And we're almost done. Let me just touch actually more on the first slide and then the data slides maybe we can get to in the question session.

Slide 46. Treatment side effects

And so some of these may be obvious, but I'll just read them out anyway. It's always important to remember that all treatments have side effects. If you look at information about clinical studies, side effects may be referred to using the terms "adverse events" or "toxicities." Some of these side effects can be immediate. So an example is having the chills or shakes when you get an intravenous infusion of a medicine like rituximab or obinutuzumab. So you're getting the medicine and this is happening immediately, right away.

Some side effects may occur days to weeks later after treatment. So, for example, a low blood count leading to an infection that might happen 2 or 3 weeks after the chemotherapy that actually caused it.

People should not assume—patients or doctors—that the new oral medications, just because they're pills and not chemo through an IV, are benign. Some of them can have very significant toxicity. And always, as a patient, request printed information that you can have as a resource for you prior to any cancer therapy you're going to get.

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Slide 47. Ibrutinib Adverse Events

DR. RAJAT BANNERJI:

This table has some of the toxicities of ibrutinib. I'm just going to skip over that in the interest of time.

Slide 48. Idelalisib Toxicity

But I will talk about idelalisib and this slide. And that's because although idelalisib again, is a simple tablet that you take at home twice a day, it has some significant side effects. So the drug has a so-called black box warning about severe diarrhea or colitis, which is an infection of the colon; damage to the liver; pneumonia; perforations or a hole in the intestine. And patients have had severe liver failure and potentially even death because of these side effects. So it's not to scare anyone away, but to just realize that some of these oral therapies can be pretty tough to get through. I would say in some cases even tougher than chemotherapy.

Slide 49. Adverse Events of Grade 3 or Higher, Safety Population

Some more tables with percentages of toxicity. But I think we want to give at least 20 minutes for questions, so let me finish up here.

Slide 50. Communication

And the last slide—important one—is regarding open communication.

Slide 51. Open Communication is Critical

And I'll go through this slide in detail. So it's critical for good care. Feel free to ask questions of your healthcare team. Ask for a clarification for anything you don't understand regarding your diagnosis or the treatment plan. Ask for explanations for anything you don't understand, including unfamiliar terms or new medications. And occasionally have—not occasionally—always have someone go with you to your appointments because occasionally—you know, I think of the old Charlie Brown cartoons in the US where when the teacher spoke to the kids, the kids only heard this wah-wah-wah sound. So sometimes you're so overwhelmed that you can't even hear what the doctor or the nurse or the nurse practitioner is telling you, and it's good to have someone else with you there who can pay attention and take notes for you and let you know what was being said.

Always feel free to ask about clinical trials or second opinions. And at such a time of great advancement in CLL, there are a lot of interesting new treatments or treatment combinations coming up, and getting early access to them in the setting of a clinical trial is a great opportunity. Your oncologist may refer you to an academic or a university medical center and that doesn't mean you're not going to be taken care of by your local doctor but that the two doctors can work together in your care.

And then I just gave two links for resources, a good place to start, the National Cancer Institute, cancer.gov website, and if you want to look at clinical studies, the clinicaltrials.gov link.

And with that I'm going to conclude my presentation, and we can go on to questions.

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Slide 52. Question-and-Answer Session

ELIZABETH KITLAS:

Thank you, Dr. Bannerji, for your informative presentation. It is time now for the question-and-answer portion of our program.

We will take the first question from our web audience. Both Kathy and Sheila would like to know the difference between CLL and lymphoma: are they two separate cancers or are they connected?

DR. RAJAT BANNERJI:

Okay, so to answer that question, CLL and lymphoma are connected. There's a type of CLL where we don't see the cells in the blood, we just see it as a lymphoma, and we call that SLL, small lymphocytic lymphoma, but practically we think of the two as the same disease. Now there are many other types of lymphomas that patients can have, so CLL would be just one type of lymphoma. But yes, it is connected to lymphoma.

ELIZABETH KITLAS:

Thank you. We're going to take our next question from our web audience: Can you discuss ibrutinib resistance? Why does this happen and about how long after using ibrutinib would this occur?

DR. RAJAT BANNERJI:

Okay, so that is an excellent question. So the group at Ohio State looked into why patients were resistant to ibrutinib, and what they saw were two different mechanisms of resistance. One was a change in the amino acid or part of the protein that the ibrutinib drug binds to on its target in the BTK protein. So the ibrutinib binds to a certain amino acid position called C481, and what they saw is that if the BTK had a mutation that changed that amino acid, then the ibrutinib drug couldn't bind anymore and would become resistant. The CLL would become resistant.

Another mechanism that they saw for resistance when this type of mutation in the target didn't occur was what we would, maybe, call a "work-around" by the tumor cell. So the tumor said okay, the BTK is being inhibited by the ibrutinib drug, but how can I still get that signal, and so they would actually have a mutation in the next step of the signal pathway, a certain protein called PLC gamma 2 or phospholipase C gamma 2. And that protein would get mutated where it was now always on, providing a signal, and it didn't need a message from BTK to turn on, it just turned automatically on. And that also is a mechanism of resistance to ibrutinib.

Now these two things that have been defined may not be the only mechanisms of resistance, but these are at least two that we understand, kind of, the science behind.

In terms of time to resistance, there was a recent study that came out from the MD Anderson group, looking at people who progressed on ibrutinib. They had about 26% of their patients stop taking ibrutinib. And about half of those patients who stopped taking ibrutinib stopped because their disease progressed. And in those patients whose disease progressed, presumably they became resistant to ibrutinib; the ibrutinib stopped working.

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DR. RAJAT BANNERJI:

There were a couple of things that they found out. The majority of those patients had a bad risk feature, and so that might have been existence of the deletion 17p or multiple genetic abnormalities that we use the term “complex karyotype” to explain, or an unmutated immunoglobulin heavy chain variable region. And so they had some features that maybe put them more at risk for more aggressive disease, and those patients typically came off treatment within a few months of therapy.

So in their experience patients who came off ibrutinib came off within about the first year of treatment, whereas the disease-free survival or the progression-free survival of ibrutinib to date has been at least about 3 years. So these patients progressed very early and came off, and these are patients likely with ibrutinib resistance.

To answer your question in summary, there are at least two mutations that are known that could lead to resistance, and it seems that if resistance occurs, it’s relatively early. So I hope that helps.

ELIZABETH KITLAS:

Thank you. And we will take the next question from the telephone audience, please.

OPERATOR:

The next question comes from Patrick in California.

PATRICK:

Hi. My question is if I was getting sick or if a patient is getting sick and goes to the oncologist and is prescribed antibiotics twice in 1 month and the doctor decides to put the patient on IVIG to treat that sickness, I heard there’s a potential risk of side effects of mini strokes. Can you give your opinion on if the IVIG treatment is worth the risk of having the mini strokes?

DR. RAJAT BANNERJI:

Right, so that brings up some of the complications of CLL that we didn’t have a chance to talk about today. And one of them is that certainly patients with CLL are at increased risk for infection. And one of the mechanisms is that their body is not making enough of the normal immunoglobulins to protect them from infection. So a doctor would do a couple of things. One is that they would get a blood test called quantitative immunoglobulins to measure the patient’s level of their natural immunoglobulins: their IgG, their IgA, their IgM. Let’s say that the doctor found those to be very low, and that is common in patients who’ve had CLL for a while. Just having that by itself wouldn’t necessarily make us treat a patient with immunoglobulin, with IVIG treatment. But then if the patient started having low immunoglobulins and recurrent infection, so in your example two different infections in the course of 4 weeks, within a month, that that would be very reasonable to treat with IVIG.

I think one of the risks we worry about with IVIG, in addition to the neurologic risk you talked about, is sometimes the protein load can be damaging to the kidneys. Patients can have reactions, allergic reactions, to the IVIG, so there are a number of toxicities. But I think if a person is starting to have recurrent infections and they have low natural immunoglobulin levels, it’s very reasonable to put them on IVIG therapy. And we know that one of the leading causes of death or mortality in CLL patients is due to infection. And so I think it’s important to be able to prevent that.

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DR. RAJAT BANNERJI:

Now in the Northeast where I am, we'll often see that patients have these recurrent infections in a seasonal pattern. And so again in the winter they're indoors, they're getting lots of infections. And so we might do the IVIG not 12 months of the year, but just through the winter months and then stop it again in the spring. But I do think that that's reasonable and the benefit in most cases does outweigh the risk of that therapy.

ELIZABETH KITLAS:

Thank you for your question, Patrick. We'll take the next question from our web audience. Brett and Emile ask what progress has or is being made in treating Richter's transformation? What is the usual course of action, and what treatments, if any, are available?

DR. RAJAT BANNERJI:

That is another excellent question. So one of our most feared complications of CLL, in the natural history of CLL, is the CLL changing to another type of lymphoma, most commonly to a lymphoma called diffuse large B-cell lymphoma, but can change to Hodgkin's disease—Hodgkin's lymphoma, or other blood cancers. And we know that when that happens, the survival of patients is much less than would have been otherwise. And so some studies look at average survival after Richter's transformation of 8 or 9 months. And our goal, if we can, for that patient is to get them into remission and if possible to get them to a bone marrow transplant, an allogeneic transplant, because that is really the only long-term way to control Richter's transformation. Even if we get into remission, if the patient—with, let's say, a chemotherapy combination—if the patient is not a transplant candidate, typically those remissions are relatively short and then they're treated again and at some point the disease becomes resistant to all treatments.

Now there's a lot of research going on. Some of it is in trying to predict which patients are most likely to get Richter's transformation. Again it's early days, but there's very good data out there that CLL that has the NOTCH mutation may be more likely to go on to Richter's transformation. And I think when we are better able to understand kind of a genetic prognostic profile that would say that this particular patient's CLL is more likely to go to Richter's, then certainly we could focus novel therapies and strategies on those patients.

In terms of new treatments for Richter's, we do know that ibrutinib has some activity in Richter's transformation. I think that if there's a clinical trial available for a patient with Richter's, that that should be a first step. But outside of that setting, typically we will use chemo-immunotherapy. And so one regimen that we use here, if the Richter's has gone to the large cell lymphoma type, is we'll use a regimen called R-EPOCH, and that's Rituxan, and then a drug called etoposide, cyclophosphamide, Adriamycin®, vincristine, and prednisone, and the chemo part of that is given as a continuous infusion for 4 days. And then on the fifth day the last drug, cyclophosphamide, is given. And so we'll use that R-EPOCH regimen to try to get them into remission, but really the goal would be, if the patient can, is to find a donor and try to get them to a bone marrow transplant once the Richter's was under control.

ELIZABETH KITLAS:

Thank you, Dr. Bannerji. We will take the next question from the telephone audience, please.

OPERATOR:

The next question comes from Melissa from Ohio.

Treating Chronic Lymphocytic Leukemia (CLL): Evaluating and Managing Options

June 11, 2015

Speaker: Rajat Bannerji, MD, PhD



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MELISSA:

Hi, Doctor, thank you for being so thorough. I just had a question in regards to the IVIG treatment. I'm currently on the treatment, so I was just wondering from your experience, what is the standard regimen for the amount of time that the treatment—how far can you go with that?

DR. RAJAT BANNERJI:

So I think in terms of how long people can be on IVIG, we've certainly had patients—and again here where I am, often we'll use it in the wintertime for people who have recurrent upper respiratory or respiratory infections—you know, we have patients who've been on IVIG for years, and all through the same months as the flu months, they'll get IVIG and they'll do it every year, on and on. I hope that was kind of where that question was going.

ELIZABETH KITLAS:

Thank you. We're going to take our next question from the web audience, and Deborah asks, you mentioned that ibrutinib acts differently from mutated, unmutated. Can you explain? And how often should you have FISH done to check for chromosomal transformation?

DR. RAJAT BANNERJI:

That's an excellent question again. So let me answer the second part of that first. And that is, we typically will check a FISH when there is a change in the clinical course of disease. So we know that the FISH profile does change over time. And to give you an example of that, we'll go back to that same deletion 17p that we talked about. And we know that in newly diagnosed patients with CLL we see that abnormality in about 7% to 10% of patients. But when we start looking at patients who've been multiply treated, that population goes up. And so when we get to people who've had three, four prior regimens of CLL, then almost 40% to 50% of patients will have deletion 17p. And the feeling is—we use a term called clonal evolution, but we think that there's probably a small part of the original CLL that has that deletion and as patients get more and more treatment, the more sensitive cells die off and that resistant 17p population grows out, and so we can detect it in more patients over time.

Any time the clinical status of CLL changes, a FISH should be done. So for example, a person had a FISH at the time of diagnosis; they've had stable disease for 4 years and now the disease starts to proliferate, and it looks like they need treatment. I would do a FISH at the beginning to see if the profile has changed.

Let's say they've been on a treatment, it's working, but now that treatment stops working. I would probably do a FISH then to see what has changed.

Now going back to ibrutinib and immunoglobulin and the heavy chain mutational status, it's very interesting with ibrutinib. It's sort of, you know, counter-counter-intuitive, if that makes any sense. When we look at CLL we think of the unmutated immunoglobulin status as being bad, to put it in simple terms, and the mutated as being good. But then when you look at how well ibrutinib works, it's actually the opposite. So when the Ohio State group published their data on the 3-year follow-up of ibrutinib therapy, they found that the patients who had an unmutated immunoglobulin had a very high complete response rate, 40%, and patients who had the mutated had a relatively low complete response rate of 6%. So even though the overall response rate, which includes patients with partial response, was equally high, it does seem that a deeper response does occur with patients with unmutated immunoglobulin heavy chain variable region specifically with ibrutinib treatment.

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ELIZABETH KITLAS:

Thank you very much. And we will take our last question from the telephone audience, please.

OPERATOR:

The next question comes from Leslie in New York.

LESLIE:

Hi, Doctor. I had a flow cytometry test done, and it came out that it was MBL. But I had a lymph node biopsied, and it was SLL. So which is more valid as far as a diagnosis?

DR. RAJAT BANNERJI:

A very interesting question, and it gets into our definitions there. So we use the term “MBL” when we see that population in less than 5,000 lymphocytes per microliter of blood in—and here’s the caveat—in a setting where there’s no other evidence of CLL. So a patient has no symptoms, they have no lymphadenopathy, etc. But in the case that you’ve just outlined, the patient has an enlarged lymph node that has CLL cells in it and a circulating population of the blood. I would consider that a patient with CLL.

ELIZABETH KITLAS:

Thank you very much. And thank you for your question, which was our final question today. Thank you again, Dr. Bannerji, for your continued dedication to leukemia patients. You and your colleagues’ research successes have made a positive impact on people’s lives.

We hope the information from this program will assist you and your family in your next steps.

Slide 53. LLS Resources

ELIZABETH KITLAS:

If we were not able to get to your question today, please call The Leukemia & Lymphoma Society’s Information Specialists at 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. Bannerji, thank you again 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 have a lovely day.

END