NHL & CLL–Diagnosis and Treatment Update

Christopher R. Flowers, MD, MS
September 13, 2012

Slide 1: NHL & CLL–Diagnosis and Treatment Update

OPERATOR:
Hello, everyone, and welcome to ***NHL and CLL–Diagnosis and Treatment Update***, a free telephone web education program. It is my pleasure to introduce your moderator Lauren Berger of The Leukemia & Lymphoma Society.

Slide 2: Welcome and Introduction

LAUREN BERGER:
Thank you and hello and hola to everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. And our special thanks to Dr. Christopher Flowers for sharing his time and expertise with us today.

We are proud to offer this program in collaboration with Abrale, our partner organization in Brazil, and Alianza Latina of Latin America.

We'd also like to acknowledge and thank Genentech and Biogen Idec for their grant to bring this program to patients.

The Leukemia & Lymphoma Society is pleased to support this program as a continuing education opportunity.

Before we begin, I would like to introduce Merula Steagall, President of Abrale and member of Alianza Latina steering committee. Welcome, Merula.

MERULA STEAGALL:
Hello, everyone. On behalf of Abrale, the Brazilian Leukemia & Lymphoma Society, I would like to thank The Leukemia & Lymphoma Society of the United States for once again enabling the Brazilian patients, as well patients from other countries in South America, to have access to this important program and receive the most up-to-date information about chronic lymphocytic leukemia and non-Hodgkin's lymphoma.

Since our establishment in 2002, The Leukemia & Lymphoma Society has been a great inspiration to us and a huge support for the improvement of all our programs.

I would like also to thank Dr. Flowers for sharing his knowledge with us. And we are sure that by the end of the program all of us will have a better understanding of how to diagnose and treat non-Hodgkin's lymphoma and chronic lymphocytic leukemia.

So thank you all for participating and for the opportunity. And a warm heart to all of you from Brazil.

LAUREN BERGER:
Thank you, Merula.

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

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JOHN WALTER:
Thank you, Lauren. I would also like to add my welcome to all the patients, caregivers, healthcare professionals on the program today. We are fortunate to have as our presenter Dr. Christopher Flowers. We appreciate Dr. Flowers's dedication to supporting the mission of The Leukemia & Lymphoma Society through his research and care of patients with blood cancer. I would like to thank him for taking the time out of a busy schedule to provide us with an update on NHL and CLL diagnosis and treatment.

The Leukemia & Lymphoma Society is committed to bringing you the most up-to-date information about your blood cancer. We know it is important for you to stay current, so that you can work with your healthcare team to determine the best options for the best outcomes.

Our vision is that one day the great majority of people who have been diagnosed with a blood cancer will be cured or they will manage their illness with good quality of life. Since 1954 LLS has awarded more than $875 million to fund research, specifically targeting blood cancers. We will continue to invest in research for cures and programs and services and improve the quality of life for patients and families. This program is one step on the road of your journey to managing your life with NHL or CLL.

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

LAUREN BERGER:
Thank you, John.

At this time I am privileged to introduce Dr. Christopher Flowers, Associate Professor of Hematology and Medical Oncology at the Winship Cancer Institute at Emory University School of Medicine in Atlanta, Georgia.

Thank you so much, Dr. Flowers.

Slide 3: Christopher R. Flowers, MD, MS

DR. CHRISTOPHER FLOWERS:
Thank you, Lauren, and thank you to The Leukemia & Lymphoma Society and to Abrale and Alianza Latina for putting together this program. And welcome and thank you to all of you who have joined us and participating today.

As Lauren mentioned, I'm Dr. Christopher Flowers, Associate Professor at Winship Cancer Institute, and I have the privilege of talking to you today from Emory University in Atlanta, and talking to you about the blood cancers.

Slide 4: Anyone can get blood cancer

As many of you are well aware, anyone can get blood cancer. And there are over a million individuals in North America who are affected each year by blood cancers.

What are shown here are data from the United States, looking at the estimated number of new cancer cases that occur. And divided by the type of cancers. And you can see in the yellow for the non-Hodgkin lymphomas, and the leukemias, including chronic lymphocytic leukemia, that these cancers represent approximately the fifth and seventh most common cancers in males and females, although these numbers vary from year to

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year. And together represent more than a million individuals who are affected each year, both in terms of new diagnoses with cancer and ongoing battles with cancer.

Slide 5: Lymphomas/Chronic Lymphocytic Leukemia
Today I will spend time talking about some forms of non-Hodgkin's lymphomas and chronic lymphocytic leukemia.

The lymphomas and CLL in general are cancers of the cells of the immune system. Shown here at the right of this slide is a cartoon that shows in green lymph nodes and chains within the lymph system, and other organs that are highly involved with the lymph system, including the GI tract and the bone marrow and the spleen.

The lymphomas and chronic lymphocytic leukemia are classified by the source of cancer cells and I will show you in a few slides some examples of that.

For the vast majority of lymphomas and CLL, the causes of these cancers are unknown. These are cancers that usually start in the lymph nodes, but they can involve any of the other tissues mentioned, including the spleen, the skin, the GI tract, the liver, the bone marrow or other sites. And oftentimes these can start in the lymph nodes and then eventually spread to one or more of these sites.

Slide 6: Common Symptoms
This patient, who is a patient from my clinic, or an example of a patient from my clinic, exhibits some of the common symptoms that can be seen with the lymphomas and chronic lymphocytic leukemia. This is a 63-year-old gentleman who was feeling reasonably well until over the last three months he started to feel much more worn down and tired, and eventually was so tired that he was unable to go to work. Over the same time period, he noted that he was starting to have sweats at night and sweats to the point where he was soaking his clothes and needing to change his pajamas. At that same time he was losing weight and lost approximately 17 pounds over the three month period.

He had noted a lump in his groin over that time period and noticed over that time period that that lump continued to get larger and larger. And by the time he came to see me, he also noticed that he was having a lump under his left arm in his armpit and in his left neck. And noted over the last several days that he was starting to feel itchy all over.

Slide 7: Common Symptoms (cont'd)
Many of these symptoms that he described are common symptoms associated with the lymphomas. And in fact, the group of symptoms of unexplained fever and night sweats and weight loss represent a group of symptoms called the B symptoms. The other symptoms that he described, a painless swelling of the lymph nodes, is very common in lymphomas. These lymph nodes enlargement is often without pain. These lymph nodes are generally movable and not tender and there are common complaints of having constant fatigue.

A relatively rare, but unusual complaint, that can occur is that when individuals, particularly individuals with Hodgkin lymphoma, drink alcohol or ETOH, that they notice immediate pain at involved lymph node sites. While this is unusual, this is a symptom that can occur.

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Itchy skin is relatively common and rashes, such as reddened patches over the skin, are also relatively common.

Slide 8: Diagnostic Evaluation
In evaluating a patient with lymphoma or chronic lymphocytic leukemia with any of those above symptoms or other symptoms that may occur, it's important to take a very good medical history to evaluate over what time period these symptoms occurred and other symptoms that may be occurring as well. And as well to evaluate other medical problems that may coexist.

It is important to do a physical exam of the lymph nodes and all other organ systems, and to perform evaluations with laboratory tests such as a complete blood count to know what the white blood cell count, red blood cell count and platelets are; to evaluate other metabolic panel electrolytes; to evaluate lactate dehydrogenase, which is used in some of the prognostic scoring systems for lymphomas to predict what the expected outcomes are of treatment; to evaluate another laboratory test, a beta-2 microglobulin that can pose a similar function in other lymphomas. Of utmost importance is performing a lymph node biopsy and I'll talk in a little bit more detail about why this is important.

Some sort of imaging testing is needed to ascertain where the lymphoma is involved, so to look to see what other lymph nodes are involved, other than the ones that can be felt or seen on exam. And that can be done with computed tomography scans or CT scans and/or positron emission tomography scans, also known as PET scans. Oftentimes these images are combined in a fused PET-CT scan. And a bone marrow biopsy is another important part of the staging evaluation, to know whether or not the disease involves the bone marrow as well.

Slide 9: WHO Classification
What's shown here is the 2001 World Health Organization Classification Schema for the non-Hodgkin's lymphomas. And this is not a slide to be memorized or to know what this classification schema is because it's one that changes over time, as pathologists discover new lymphomas and change the diagnoses from older lymphomas that may divide into new categories. This has been updated to 2008 and now has even more classifications that cannot fit onto one slide. And there now are at least 61 different varieties of non-Hodgkin's lymphomas and other varieties of Hodgkin lymphomas that should be subdivided as well.

And this is meant to show the diversity of these lymphoma subtypes. I will focus on three of these today, but each of these lymphomas should be specifically classified and may require specific treatments that are individual to the specific classification scheme.

Slide 10: Excisional Biopsy Improves Accurate Diagnosis
I mentioned earlier that it is important to perform a biopsy to determine the type of lymphoma that is seen. What's shown here is an example or a cartoon of a lymph node on the left, with the different areas that are found in a normal lymph node. And for each of those areas found in a normal lymph node, different kinds of lymphomas can arise.

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You can imagine if a doctor takes a needle and sticks a needle into that lymph node and draws back some fluid and some tissue and some cells and looks at those cells underneath a microscope and then does additional tests on those cells, those might be able to tell you that a patient has lymphoma. But drawing back the fluid and drawing back tissue doesn't tell you exactly what part of the lymph node that came from and what the other architecture of the lymph node is. And so for that reason it's necessary to do an excisional biopsy where all of the lymph node is taken out or at least a large portion of the lymph node is taken out, so you can not only see the cells that are abnormal, but also see the architecture of the rest of the lymph node to know what parts of the lymph node are normal and abnormal.

For those reasons an excisional biopsy really provides the best information for coming up with a specific diagnosis of lymphoma and to be able to form a classification according to the World Health Organization Classification System.

Slide 11: Graphic

This slide shows an example of a CT scan of a patient's chest who has lymphoma. Shown here, the top portion of the slide, is the front of the body, so the portion where the belly button might be farther down from the chest. The top white portion shown at the front of the top portion of the slide is the sternum. The white portion at the back shows the spinal column. And the middle black portions of the slide are the two lungs.

What is abnormal here is right behind the sternum or the white portion, shown at the front of the slide, is an area that should not be there and that is involvement with lymphoma.

When a physician performs a CT scan or a PET-CT scan, these types of images are used to try and identify abnormal regions on the scan that will help with identifying where lymphoma is involved in the body. And these are the types of images that you as patients and as caregivers should ask your providers to show you to help in understanding exactly where the lymphoma is involved.

Slide 12: Ann Arbor Staging System

In addition these scans help to identify what stage the lymphoma is at diagnosis. Shown here is the Ann Arbor Staging System, where lymphomas are divided into four stages. Stage I, involvement with a single lymph node or single lymph node area. Stage II, involvement with more than one lymph node area, but on the same side of the diaphragm or on the same half of the body, either on the top half, most commonly, or sometime on the bottom half of the body. Stage III would show evidence of involvement on both halves of the body, so both above and below the diaphragm. And stage IV indicates involvement outside of the lymph node areas to other organs like the bone marrow or the spleen. Excuse me, the bone marrow or another organ.

The Stage IV diagnosis or determination means that it is really necessary to perform a bone marrow biopsy to have complete staging evaluation.

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Slide 13: WHO Classification

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I will spend most of the rest of the time talking about three particular lymphoma diagnoses within the World Health Organization Classification: diffuse large B cell lymphoma, follicular lymphoma and chronic lymphocytic leukemia or small lymphocytic lymphoma. These are two different diagnoses which we now know are part of the same disease. We call this disease CLL or chronic lymphocytic leukemia when we first find it in the blood or the bone marrow and we call it SLL when we first find it in the lymph nodes.

Slide 14: Diffuse Large B-Cell Lymphoma

First I will talk about diffuse large B cell lymphoma. Diffuse large B cell lymphoma or DLBCL is the most common type of non-Hodgkin lymphoma and approximately 30% or one-third of individuals who have non-Hodgkin lymphoma have diffuse large B cell lymphoma. This can be a very aggressive behaving lymphoma if left untreated, and the average survival is weeks to months if it's left untreated.

The flip side of that is that this is a lymphoma that is very curable with standard therapies that we use commonly. This is a disease that grows rapidly and because chemotherapy kills cells that grow rapidly, the common uses of rituximab plus CHOP chemotherapy cures about 50% or more of individuals who have this diagnosis.

One of the other things that that also indicates, though, is that outcomes for patients with diffuse large B cell lymphoma can be quite variable and I'll talk in a little bit more detail about some of the things that we now know about why that might be.

I mentioned earlier that B symptoms are something that often occur for patients with lymphomas and about a third or more of individuals with diffuse large B cell lymphoma have those B symptoms of fevers, night sweats and weight loss. This is a disease that can sometimes present outside of the lymph nodes and commonly presents under the microscope as is shown on the right half of the slide, with large cells that grow in a diffuse pattern, and that gives diffuse large B cell lymphoma its name.

Slide 15: DLBCL Management Strategy

This is a very complex slide, but one that shows the general management strategies that physicians use in terms of identifying the best ways to treat patients with diffuse large B cell lymphoma.

As I mentioned earlier, these lymphomas can be divided into those that have limited stage disease, stage I or stage II, where radiation often plays a role in the management, that's indicated on this slide by RT. Or they can be divided into those with advanced stage disease, stage III or stage IV, where radiation often plays less of a role.

As I mentioned, the standard approach for management of patients with diffuse large B cell lymphoma now involves the combination of three chemotherapy drugs: cyclophosphamide, Adriamycin®, which has another fancy name that begins with an H, Oncovin® or vincristine, and a steroid pill prednisone, which is used in combination with rituximab. And that's R-CHOP or the acronym for this regimen, is a commonly used approach.

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While this approach is used in the front-line setting, patients with diffuse large B cell lymphoma may have their lymphoma come back. When this disease comes back, it can still be cured with additional chemotherapy and with autologous peripheral blood stem cell transplantation. There are other options for patients who fail either one or both of these regimens, that can include some of the new agents that I'll discuss in other parts of the presentation.

Slide 16: Advances in Treatment

This slide here shows in a graphical fashion what we can expect for some of the outcomes for patients with diffuse large B cell lymphoma. Shown at the left-handed slides are different chemotherapy options that have been used in the past for diffuse large B cell lymphoma. On the Y axis, going up and down, are the percentage of patients who are alive at any given time point. Over the X axis, or going across, are the years after the treatment was given that shows how many patients were alive at that time point. What you can see on the left-hand side of the slide, the CHOP therapy was a standard therapy that was used since the 1970s. From the 1970s until the 1990s, there were a number of different chemotherapy options that were developed and those are listed there with different colors on the slide. M-BACOD, MACOP-B are two of those regimens, and my favorite name for any chemotherapy regimen of all time, ProMace/cytaBOM, is shown there as well.

What you can also see from that part of the slide is that despite all these changes in chemotherapy regimens, even with these more aggressive chemotherapy regimens, that there were no differences in survival when compared to CHOP.

What you can see on the right half of the slide is that with the addition of rituximab to CHOP chemotherapy, shown in the yellow curve, that there were improvements in survival. And these are additional follow-up on the study that was published first in 2002 that show with additional follow-up that those benefits in survival continued and continued to improve in comparison to CHOP therapy.

The other thing that you can see on this curve is that there is a flattening of the curve after approximately five years, with patients no longer dying from their lymphoma at that time point, suggesting that there is a cure of this disease, for patients who have lived five years and have not had their disease come back.

As I mentioned earlier, diffuse large B cell lymphoma can have quite heterogeneous outcomes. And while diffuse large B cell lymphoma can be cured for about half of individuals, at diagnosis it can be difficult to determine which patients fall into the half that can be cured with standard therapy as opposed to those who are not likely to be cured. But inroads into the development of new research for diffuse large B cell lymphoma, some of which has been funded by The Leukemia & Lymphoma Society, have helped us to discover new ways of diagnosing these lymphomas and new ways of using that more detailed information to help to treat patients who we would not expect to be cured.

Slide 17: Genetic Testing

Shown here is a complex diagram, but across the X axis or horizontally back and forth, are lymphoma biopsies. And each of these lines represents individual patients with diffuse large B cell lymphoma. All of those patients' diffuse large B cell lymphoma looks exactly the same under the microscope, as represented by the box at the

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top. Shown on the Y axis of the slide, or going up and down, are different genes that are associated with diffuse large B cell lymphoma. And now we've done testing, something called gene expression profiling, that helps to identify the genes that are associated with diffuse large B cell lymphoma.

Shown in red are genes that are more active in particular patients' lymphomas and shown in green are those that are less active.

What you can see here is that there are certain diffuse large B cell lymphomas, although they look identical to other ones under the microscope, that have genes that are activated and look like normal activated B cells and these have been called ABC-like or activated B cell-like diffuse large B cell lymphoma, while there are others that look like germinal centers, and these have been called GCB-like diffuse large B cell lymphoma.

Slide 18: Gene Expression

We know that these differences in the genes in diffuse large B cell lymphoma not only have importance in terms of determining the biology of those lymphomas, but that biology is related to differences in outcomes. You can see here at the bottom of this slide another survival curve. And what this survival curve shows is that while about half or more of individuals with GCB-like diffuse large B cell lymphoma are cured of their lymphoma or are alive ten years out, without evidence of their lymphoma coming back, only about 30% of those with ABC-like diffuse large B cell lymphoma have that same outcome, suggesting that we need to come up with newer therapies for these subtypes of diffuse large B cell lymphoma.

Slide 19: GCB vs Non-GCB Subtypes of DLBCL

Well, gene expression profiling is something that is difficult to do for most patients across the world. We've now come up with newer techniques to be able to perform the same kind of segregation into different kinds of diffuse large B cell lymphoma, with easier to use techniques like stains. Shown here at the left of the slide are different stains that can be used on the actual slide, CD10, BCL6 and MUM1. Using these stains we can help to identify which patients have GCB-like diffuse large B cell lymphoma and which ones have non-GCB, which tend to be the ABC-like diffuse large B cell lymphoma. While this is not quite as accurate as gene expression profiling, this helps in terms of identifying patients who are expected to do better or do worse.

Well, this is something that has not really been uniformly applied to patients, in part because although we can help to identify which patients have the better risk or worse risk diffuse large B cell lymphoma, as of yet we don't have specific treatments that we can use for those particular patients.

Slide 20: Using DLBCL

What we are now doing are developing clinical trials, one of which I've helped to develop and that we are participating in at Emory, to try and identify those patients who are expected to do worse with standard therapy, and then apply newer therapies that may help to improve outcomes for those patients. And this just shows one example of a trial from our work, where we are taking patients who have been identified to have the non-GCB subtype, most of which are ABC-like diffuse large B cell lymphoma, and then patients are randomized in a clinical trial to either receive R-CHOP, which would be the standard therapy that they would

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get outside of the trial, or to have another drug added, bortezomib, which appears in earlier trials, that have not been randomized, that may improve outcomes for patients with the ABC subtype.

Slide 21: Monograph graphic

And this raises the importance of participating in clinical trials, particularly for lymphoma subtypes that are not curable with standard therapy or expected to have poor outcomes like the ABC subtype.

Our group has been very involved in the study of diffuse large B cell lymphoma, in particular to junior investigators who are up and coming researchers in diffuse large B cell lymphoma, Loretta Nastoupil and Rajni Sinha, have been very involved in trying to understand the treatment strategies that are currently used for diffuse large B cell lymphoma, understanding which ones are effective and which ones have been less effective, uncovering those agents that are new treatments or novel agents that can be used in diffuse large B cell lymphoma, and coming up with new strategies that help to improve outcomes for patients with diffuse large B cell lymphoma.

Slide 22: Finding Causes for Lymphoma

In addition to trying to uncover ways to treat patients who already have a diagnosis, we're trying to uncover reasons for why patients get diffuse large B cell lymphoma in the first place. What's shown here is a map of the state of Georgia, with highlighted, those places where patients are more likely to occur – or individuals in the population are more likely to have non-Hodgkin lymphoma and those who are more likely to have diffuse large B cell lymphoma, and to be able to not only track who those individuals are and how this has occurred, but trying to identify causes for why this occurred. And this type of research will help us ultimately to prevent the lymphomas from occurring in the first place.

Slide 23: Follicular Lymphoma (FL)

Next I'm going to turn my attention to follicular lymphoma. This is the second most common type of non-Hodgkin lymphoma and accounts for about a quarter of non-Hodgkin lymphomas in North America. This is a disease that can be more variable in its presentation and can grow quite slowly over time. Because it grows quite slowly over time, typically patients present with advanced stage disease, so with Ann Arbor stage III or stage IV. Often patients do not have symptoms at the time that they're diagnosed. However, because this is a more slow-growing lymphoma and for other reasons that are less well understood, follicular lymphoma is not curable with standard therapy.

Patients with follicular lymphoma typically respond to therapies like R-CHOP and other therapies and can have their lymphoma go away and can have it stay away for a prolonged period of time. But these are lymphomas that tend to come back over time.

Slide 24: Overall Survival According to FLIPI

If you look at the internet or look at other literature out there, the quoted median survival for patients with follicular lymphoma, or quoted average survival, is about ten years. However, this is a difficult statistic to really interpret because in order to know that the average survival is about ten years, it has to be based on therapies

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that we were using ten years ago. With current modern therapy we expect that to be much better, with types of treatment we are using now, but it'll take additional years of follow-up with these treatments to know what the outcomes really are. And by that time we will have newer treatments for follicular lymphoma.

As of yet there is no definitive standard of care for patients with follicular lymphoma and there are a number of different treatment options that can be used at diagnosis and at relapse.

An important thing to consider for follicular lymphoma is trying to identify factors that help to predict what outcomes might be. As I showed you for diffuse large B cell lymphoma with subtyping the lymphomas, there are ways to do that in predicting outcomes for patients with follicular lymphoma. As of yet the most common way for doing that is using different clinical factors like the number of nodal regions involved, the LDH or lactate dehydrogenase that I mentioned is an important laboratory test to have performed at diagnosis, the age of the patient, the stage and the hemoglobin value.

Using those different factors, you can help to identify the Follicular Lymphoma International Prognostic Index score or FLIPI score, and patients can be grouped into one of three groups: a low risk group, an intermediate risk group, and a high risk group, based on the number of factors that occur.

You can see at the right half of the bottom part of the slide, that using those FLIPI risk groups, we can help to predict what the expected five year and ten year overall survival is for patients, which can vary quite dramatically. For patients who fall into that FLIPI high risk group, those are patients where it's appropriate to consider clinical trials and newer and more experimental regimens that may hopefully help to change those expected outcomes of five years and ten years.

Slide 25: A Management Approach for FL

However, as I mentioned, the management for follicular lymphoma can be quite diverse. The initial evaluation should occur using the kinds of testing that I mentioned at the beginning of the presentation. Patients can be grouped into those who have localized disease, which is relatively uncommon, those who have advanced stage, but a low tumor burden, and those that have advanced stage disease and a high tumor burden.

For many of those patients who have advanced stage disease and a low tumor burden, an appropriate management course can be observation. Now while this sounds quite unusual for someone to have a diagnosis of cancer, to know that they have cancer, and then for the doctor to recommend that you should just observe and not do anything, this is an appropriate management strategy for patients with follicular lymphoma and other low grade lymphomas. That is in part because older clinical trials that compared older chemotherapy regimens to observations showed that patients who observed and then got chemotherapy did not have any difference in survival than those patients who had chemotherapy right away. What is not as well known is how observation compares to newer and more modern approaches, but observation is still an appropriate management strategy for those who have low tumor burden.

Slide 26: Criteria for Initiation of Treatment: Indolent NHL

For patients who have advanced stage disease with a greater tumor burden, there are a number of treatment options that are available. Shown here are the criteria for initiation of treatment for patients who have low

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tumor burden and are observed or the criteria for initiation of therapy and the criteria that constitutes a high tumor burden. These have been defined in a number of ways by the British group, which is not shown here, by the French group, which is shown here as the GELF criteria, and by the National Comprehensive Cancer Network of the United States. Listed here are some of the criteria, having a number of nodal sites involved, having a lymph node mass that is greater than 7 centimeters, having symptoms related to the lymphoma, having a large spleen that is greater than 16 centimeters, having fluid backup on the lungs or in the belly, noted by pleural effusions or ascites, having a low white blood cell count or low platelets, or having circulating lymphoma cells listed there as leukemia. Those would all be reasons to start treatment in a patient who's undergoing watchful waiting or to start treatment in a patient who's newly diagnosed.

Slide 27: Rituximab (R) Compared with a "Watch and Wait"

I mentioned that for patients with follicular lymphoma who have no symptoms at diagnosis or for those who have a low tumor burden, it is appropriate to consider watch and wait or to observe at diagnosis. I also mentioned that with newer, more modern therapies like antibody therapies like rituximab, it is less well known how those compare in terms of survival.

What are shown here are data from a study that has not yet been published, but has been presented by the British group at national meetings of experts in hematology, that compared observation to rituximab therapy. This shows that patients who had rituximab, shown here either as four weekly doses or four weekly doses followed by a maintenance period of rituximab, given once every two months for two years, that those individuals had improvement in what's called progression-free survival at three years.

Now this seems to be a benefit for patients, but it's not surprising that patients who had an active therapy did better in terms of slowing the progression of their disease or preventing progression of disease, than those who were observed.

Another endpoint that was used in this trial was looking at the time to when they needed another treatment. For patients who were observed that was approximately three years. For patients who had one of the two rituximab-based approaches, that has not yet been reached at the time of follow-up in this trial. Suggesting that patients are staying off of additional therapies for a much longer time. Which is a benefit to patients. And it needs to be compared to what the additional challenges may be with receiving an up-front therapy or receiving an up-front therapy followed by maintenance therapy. And those are the kinds of decisions that need to be weighed by patients and caregivers and their treating physicians.

Slide 28: Adding Rituximab to Front-Line Chemo

I also mentioned to you that for patients with more advanced stage disease with a high tumor burden, that there were a number of treatment options. What this slide shows is that there are a number of based chemotherapy regimens that can be used. So chemotherapy with CHOP I mentioned for diffuse large B cell lymphoma, that can also be used for follicular lymphoma. There are other chemotherapy regimens that have been used across the world, using other chemotherapy agents in combination.

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What this slide shows is that regardless of what type of chemotherapy is given, giving that same chemotherapy with rituximab provided benefit in terms of complete response and in some trials, shown there with an asterisk to the right of the number, that there was a benefit in terms of overall survival that was statistically different from the group that received chemo alone. What that suggests is that in the modern era that all patients who are treated with a chemotherapy-based approach, who can tolerate rituximab, should receive rituximab with their chemotherapy.

Slide 29: Rituximab Maintenance vs Observation

Around the same time that we were doing those clinical trials across the world, looking at rituximab with or without chemotherapy, or looking at chemotherapy with or without rituximab, there were other trials that were looking at the role of maintenance therapy following chemotherapy. What remained as a question was if you got rituximab with your chemotherapy, was there still a benefit to giving maintenance rituximab afterwards. And that question was answered by this clinical trial, that was led by the French GELA group.

This was a trial that allowed different institutions to use different kinds of chemotherapy, shown there in the blue box, where that chemotherapy was given with rituximab, and then patients who responded were then randomized to receive rituximab given as a maintenance therapy, where one dose of rituximab was given every two months for two years, or patients were observed.

What's shown at the bottom of the slide is that when you compare the progression-free survival for patients who received rituximab maintenance to those who were observed, that there was a benefit to receiving rituximab maintenance, even if rituximab was given with the chemotherapy in the up-front setting.

These different approaches now constitute the standard of care for the initial treatment for patients with high tumor burden. Rituximab with chemotherapy should be given, followed by rituximab maintenance for patients who can tolerate, if progression-free survival is considered to be a meaningful endpoint by both the clinician and the patient.

What is less well known is what kind of chemotherapy is the optimal chemotherapy to give because those were not compared in this trial and have not really been well compared in a modern trial.

Slide 30: Relapsed Follicular Lymphoma

For patients with follicular lymphoma who have their lymphoma come back, there are a number of different treatment options. And I think the first question to consider is whether treatment is absolutely necessary, once you go back to the GELF or BNLI, the British, or the National Comprehensive Cancer Network criteria that I mentioned earlier, to determine whether treatment is necessary, and to look at the clinical situation to determine what type of treatment is the best option.

Slide 31: Recurrent Follicular Lymphoma

There are a number of conventional treatments that can be available, including some of those that I mentioned, treatments that are used – that are not used at diagnosis could potentially be treatment options at relapse. Stem cell transplant can sometimes be an option for patients. And I think it is always important to consider

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the role of clinical trials for patients with these types of lymphomas because they are not cured with standard therapy.

Slide 32: B-Cell Receptor Signaling

Next I will highlight some of the key data in clinical trials that are emerging for patients with follicular lymphoma and other lymphomas, that highlight some of the exciting areas of research currently.

One of the things that we are now learning more about are the ways that lymphoma cells have signaling mechanisms to help them to maintain survival. And much of this comes through a signaling pathway through a receptor on the surface of the B cell. Follicular lymphoma and other lymphomas that we have talked about today arise out of the B cells, and interrupting B cell signaling may be a way to help kill these lymphomas that otherwise find a way to stay alive.

One drug that has been used in this particular area is a drug that is a SYK-inhibitor or interrupts part of this pathway, shown on the last slide.

I'll just go back briefly to show you parts of the signaling cascade and part of this involves SYK, shown as SYK at the left-most portion of the slide.

Two other portions that I will highlight are BTK and PI3K, shown here, which are other parts of the signaling pathway.

Slide 33: SYK Inhibition: Phase I Results

Shown in this slide we can see that there are a number of different lymphomas that have been tested, using a particular drug to inhibit SYK or this part of the pathway. And there have been testing of follicular lymphoma to suggest that this is an active drug for patients with follicular lymphoma. And additional trials are ongoing.

Slide 34: Phase I Results BTK Inhibitor: PCI-32765

Another pathway that has been looked at is BTK or Bruton's tyrosine kinase. And there's a particular inhibitor, PCI-32765, whose name has been so long that we've now finally given it a name, or ibrutinib, which appears to be active in follicular lymphoma and other lymphomas. You can see here in the most early phases of clinical trials, Phase I clinical trial, that about 40% of individuals who had follicular lymphoma responded to this drug as a single agent.

Slide 35: Adverse Events: PCI-32765

The other thing to note about inhibitors of this pathway are these are drugs that appear to be well tolerated and don't have the same kinds of side effects that we see with chemotherapy. Shown at the left portion of the slide are all the side effects or adverse events that were seen in this trial for all patients. And the most common of these events were events that fall into the category that we would call grade 1 or of limited severity. You can see that there were relatively few events that were grade 3 and no grade 4 events in terms of the most common events.

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DR. CHRISTOPHER FLOWERS:

And we looked at the ways that these drugs, or this drug in particular, affect the blood count system. So thrombocytopenia shown there or the effect on the platelets, neutropenia shows the effect on some of the white blood cells, and anemia indicates the effect on the red blood cells. But these effects were relatively limited in terms of the number of patients or percentage of patients that were affected in this way.

Slide 36: Treatment-related Lymphocytosis: BTKi

The other thing that we're learning from clinical trials is that these drugs work in new and very interesting ways. So what's shown here in the graph and in the picture is that one of the things we can see is that these drugs affect a shift in the lymphoma cells, from lymph nodes into the bloodstream. So shown at the right of the picture from day one to day two, you can see very rapid shrinkage in the lymph node in this particular patient who participated in this trial. What you also see, shown at the left portion of the slide, are the blood counts, shown on the Y axis, going up and down, and the number of days since treatment. And you can see that the blood counts actually shot up in terms of the number of lymphoma cells that were in the bloodstream on the days following chemotherapy. Those shot up initially with a shift from the lymph nodes into the bloodstream, but over time those numbers of white blood cells that were involved with lymphoma went down, suggesting that there may be a new kind of phenomenon with these agents, and a phenomenon that may be well suited to combining them with chemotherapy, where we see the shift with an agent like the BTK inhibitor and then use chemotherapy to kill the cells once they're into the bloodstream.

Slide 37: GS-1101 Tumor Shrinkage in Indolent NHL

And this just shows an example of another agent, one of the PI3K inhibitors or GS-1101, another name for this is CAL-101. And this is what's called a waterfall plot, that shows number of patients, each one of the bars going up and down is an individual patient, and it shows the tumor shrinkage for that individual patient. And you can see for the majority of patients who were treated on this clinical trial with different forms of low grade lymphoma or low grade non-Hodgkin lymphoma, that their tumors did shrink. For some of those patients it did grow, shown on the left portion of the slide, and the therapy did not work, but for many of them it was a therapy that produced shrinkage.

And these are other ways to the early assessments of new drugs to determine whether they might be effective or might be promising for testing in other clinical trials.

Slide 38: CLL Staging Systems

Finally, I'm going to turn to chronic lymphocytic leukemia or CLL. Like the lymphomas, CLL has its own staging system. For patients with CLL in the United States we commonly use the Rai stating system that was developed by Kanti Rai, that is broken down into four stages and a Rai zero stage for patients who have only evidence of circulating cells and no evidence of large lymph nodes. And you can see shown on the right portion of the slide, the expected survival for patients as it was originally defined in 1972 by Dr. Rai.

What we see in the modern era is that using the Rai staging system, that these stages still predict for survival, but there have been improvements in survival, particularly for patients with more advance stage disease.

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Slide 39: CLL Overall Survival

DR. CHRISTOPHER FLOWERS:
And that's shown here. The Mayo Clinic, led by Tait Shanafelt, did a repeat analysis of the Rai staging system and you can see that for patients who fall into those more advanced stage diseases, stage III and stage IV, those are individuals who have improved survival compared to the original Rai staging in the 1970s.

The Rai staging also helps us to define patients and levels of hemoglobin and platelet count when it's appropriate to start treatment.

Slide 40: Previously Untreated CLL Treatment Options

Shown here are a timeline for patients' treatment options for CLL from the 1960s up until 2000. In the early management of chronic lymphocytic leukemia and small lymphocytic lymphoma, chlorambucil and alkylating agents were the predominant means of treatment. That continued into the 70s and it wasn't until the 80s that other drugs like fludarabine and other purine nucleoside analogues emerged as very effective treatment for CLL.

These were later combined in the 1980s – or 1990s – and you can see here that purine nucleoside analogues and alkylators became a predominant treatment option. Randomized controlled trials were used, predominantly led by the German CLL Study Group, where they compared the combination of fludarabine and cyclophosphamide to fludarabine alone or to cyclophosphamide alone in other trials. And who suggested that combination therapy was better than the agent – a single agent therapy.

Later, following the use of rituximab, that was added to chemotherapy, and now FCR has emerged as one of the standard chemotherapy regimens for patients with newly diagnosed CLL, using the combination of fludarabine, cyclophosphamide and rituximab.

Other antibody therapies have also emerged and those include alemtuzumab and ofatumumab, and newer agents have also emerged like bendamustine, that add to the arsenal of treatments that we can use for patients with chronic lymphocytic leukemia.

Slide 41: Traditional Prognostic Factors

Like follicular lymphoma and diffuse large B cell lymphoma, there are factors that we can use to predict what outcomes would be or to predict survival. Some of the more traditional factors have been based on clinical scenarios like stage, how rapidly the lymphocyte count is doubling, so if it's doubling in less than a year, the amount of bone marrow involvement, age, gender. And now with newer data we're able to look at the genes that are associated with chronic lymphocytic leukemia to help to predict survival.

Slide 42: Newer Prognostic Factors

Shown here are some of these newer prognostic factors. So 17p deletion or 17p minus or involvement with the P53 gene are one of the worst or most unfavorable prognostic factors. There are other genetics that can be determined by FISH analysis of the bone marrow, which help to identify what an expected survival would be with chronic lymphocytic leukemia.

In addition, there are a number of other tests that can be used that can help with this process.

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Slide 43: Newly Diagnosed and Relapsed/Refractory CLL Patients

DR. CHRISTOPHER FLOWERS:
As I mentioned, there are a number of different regimens that can be used for patients with newly diagnosed and relapsed chronic lymphocytic leukemia. The FCR regimen I mentioned. There are other nucleoside analogues like pentostatins, that have been used in the PCR regimen. And for patients who have had a good response to first-line therapy, sometimes those same therapies can be used when the disease comes back. And there are additional treatments or treatment combinations that can be used.

Here again I would like to highlight the role of clinical trials for patients with relapsed and for patients with newly diagnosed chronic lymphocytic leukemia. Because this is also a type of lymphoid malignancy that cannot be cured with traditional treatment options, clinical trials are appropriate, both at diagnosis and at relapse of this disease.

Many of the agents that I discussed earlier, the BTK inhibitor, CAL-101, NPI3 kinase inhibitors, also have opportunity in chronic lymphocytic leukemia.

Slide 44: New Side Effects with New Therapies

Like I mentioned earlier, there are also newer reactions that we have seen with – in therapies with new clinical trials for CLL. This is a unique and odd reaction that we have seen with lenalidomide in clinical trials for CLL and with other agents as well. This phenomenon of a tumor flare reaction that occurs after start of the chemotherapy drug was a strange one and one that fortunately brave investigators identified. What was seen is that after starting therapy with lenalidomide, the patient's tumor nodes actually grew. And that's shown on the slide by the patient's neck at the left side, where the tumor actually increased in size after starting therapy. What was also noted was that this was red and warm and tender, which would be relatively unusual for a lymphoma or CLL lymph node.

Fortunately for this patient and for patients in general, the investigators continued therapy despite this increase in the lymph node, and what you can see is that over time that lymph node actually shrunk. This likely represents a flare of the tumor with infiltration of immune cells going there to fight the tumor, that may be stimulated by the treatment.

Shown at the bottom is another example of tumor flare on a CT scan, where the place with the arrow shows a lymph node that was enlarged at the initial treatment, it increased in size with treatment, and it eventually after treatment went down to where it was not seen at all.

Slide 45: Patient-Clinician Communication

One factor that I think is extremely important for all patients who are involved in care of lymphoma and CLL is effective communication with their physician and with their care provider team. In orchestrating the patient and physician communication, it's important to use approaches that are tailored to individual needs in terms of health literacy and numeracy. These are factors that are important for clinicians and care providers to consider. And to consider language barriers and decision-making capacity of the patient and their care providers.

DR. CHRISTOPHER FLOWERS:
It's very important for patients to receive clear and for physicians to provide clear written instructions about when and how to contact practitioners. It's important that coordination of care among providers is essential, not only with the oncologist or hematologist that is treating the lymphoma or leukemia, but also with other care providers that may help with other aspects of your care. And for patients and care providers it's important to receive and give written and/or electronic copies of management plans and of scans and other instruments.

So with this I'll close and I'm happy to take questions.

Slide 46: Question and Answer Session

LAUREN BERGER:
Thank you so much, Dr. Flowers, for a very clear and informative presentation. It is now time for the question and answer portion of our program.

We'll take the first question from our web audience. Ronald asks, "Are there any more clear or definitive criteria for differentiating indolent versus aggressive in CLL?"

DR. CHRISTOPHER FLOWERS:
The FISH criteria that I mentioned are probably the best existing criteria to help to define indolent or aggressive CLL. There are newer exploratory criteria that are being developed by a number of investigators, looking at things like gene expression profiling, like I showed you for diffuse large B cell lymphoma. As of yet, the 17p deletion by FISH is the best means to identify the worst prognosis or the most unfavorable behaving chronic lymphocytic leukemia patients. And those patients perhaps should pursue different treatment options from the general treatment options that I mentioned. And consider things like allogeneic peripheral blood stem cell transplantation. But in general, other than those mentioned, which are gaining in use across the world, the newer and developing systems have not gained broad use for helping to differentiate patients with chronic lymphocytic leukemia.

LAUREN BERGER:
Thanks for that question, Ronald. We'll take the next question from our Spanish-speaking audience, please. And we have a question from Joaquim, a patient, who asks, "Can people bank their own stem cells while in remission for later use? And if yes, do they last indefinitely or is there a time limit for use?"

DR. CHRISTOPHER FLOWERS:
Thanks, Joaquim, for that excellent question. So the question relates to the banking of stem cells for later use. The use of stem cells or use of one's own stem cells is most appropriate in autologous peripheral blood stem cell transplantation. There are a number of non-Hodgkin lymphoma subtypes and Hodgkin lymphoma uses, where giving back one's own stem cells is appropriate. And that is typically done after high dose or dose-intensive chemotherapy. As I mentioned in the program, for diffuse large B cell lymphoma, that is one of the potential treatment options for patients who relapse after initial therapy with R-CHOP.

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DR. CHRISTOPHER FLOWERS:
Most commonly stem cells are collected prior to the autologous peripheral blood stem cell transplantation and so it would be uncommon for stem cells to be banked. This does, however, occur in situations where radiation might occur to the bone marrow or some other event might occur, where you would expect that stem cells might not be able to be collected in the future. But for the vast majority of patients, stem cell collection and storage is not something that is routinely done or necessary.

LAUREN BERGER:
Thank you for that question and that response. We'll take the next question from our audience in Brazil and a patient named Sonja asks, "How effective is a mini-transplant for a CLL patient if other treatments do not help any more and until what age?"

DR. CHRISTOPHER FLOWERS:
Mini-transplantation for chronic lymphocytic leukemia goes by a number of names. This is also called non-myeloablative allogeneic peripheral blood stem cell transplantation or reduced intensity conditioning stem cell transplantation. Like its many names, there are many different ways of performing this kind of transplant and those vary from center to center. And with each of those different approaches there are different outcomes. But in general for patients who have relapsed or refractory chronic lymphocytic leukemia that is not responding to other therapies, giving additional chemotherapy provides minimal benefit. One particular example of a patient population where this occurs are in patients who are refractory to fludarabine-containing regimens or not responding to fludarabine. Those patients would have an expected survival of approximately ten months or less. Likewise patients who have 17p deletion, who are not responding to therapy, would have poor expected outcomes as I mentioned.

For those patients and for other patients where allogeneic stem cell transplantation is appropriate, data grouped together from a number of different clinical trials suggest that approximately 20 to maybe as high as 30% of individuals who go on to have a mini-transplant can have long-term disease-free survival with that approach.

LAUREN BERGER:
Thank you for your question, Sonja. We'll take the next question from the web audience and a patient named Herbert asks, "I was recently diagnosed with follicular lymphoma. My oncologist told me I will not need treatment for five to seven years. Are there advantages to treatment now instead of waiting?"

DR. CHRISTOPHER FLOWERS:
So this is a very difficult question and thank you, Herbert, for that question. I mentioned part of this in my discussion about the recent clinical trial comparing rituximab to observation. I also mentioned that it is sometimes challenging for both patients and physicians to hear that there is a diagnosis of lymphoma and choose not to do anything. It is very difficult as of yet to predict what the time of watchful waiting will be. In the largest studies that have looked at this, studies from Stanford and studies that I mentioned from the British group, have shown that the average time of watchful waiting is about three years. But predicting what watchful waiting is for any given patient is very difficult, or how long that watchful waiting period would be.

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DR. CHRISTOPHER FLOWERS:
Watchful waiting is something that if should continue until one of the GELF criteria that I mentioned or one of the NCCN criteria are met, as a reason to start treatment, and once one of those is met, treatment should start, regardless of how long it takes.

The data that I mentioned from the British group suggests that there may be some benefit to starting rituximab up front as opposed to starting on watchful waiting course or an observation course. To really know what those differences are would need involve clear differences in overall survival and as of yet those trials have not followed patients for long enough to know that that difference exists.

LAUREN BERGER:
Thank you for that response. Dr. Flowers, earlier you mentioned the phrase "high tumor burden." Can you give us a little explanation of that, please?

DR. CHRISTOPHER FLOWERS:
Sure. High tumor burden is a phrase that has come into being to try and help group patients with follicular lymphoma, who have advanced stage disease, which is the majority of patients, into those who need treatment immediately when they're diagnosed, as opposed to those for whom watchful waiting may be an appropriate option. For patients who have high tumor burden follicular lymphoma, watchful waiting is not an appropriate initial option for the majority of patients. And high tumor burden is determined by those GELF criteria. So having a single lymph node that is greater than 7 centimeters, having more than three lymph nodes, each of which is greater than 3 centimeters, having involvement with an organ or threatening of an organ by a lymph node, having lymph nodes that are causing symptoms or disease that is causing symptoms like fevers, night sweats or weight loss, or having this provide some kind of compromise on the bone marrow or on the normal blood counts.

LAUREN BERGER:
Thank you, appreciate that explanation. We'll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Stephanie in Florida.

STEPHANIE:
Yes, for the situation of diffuse large B cell lymphoma, mediastinal primary, what is the best attempt for biopsy? Is it mediastinoscopy or mediastinotomy?

DR. CHRISTOPHER FLOWERS:
Mediastinoscopy is likely to be the most commonly used approach for the management of a mediastinal primary for diffuse large B cell lymphoma. But really the optimal approach for a given patient depends upon the surgeon, the surgeon's skill with each of the procedures, the location and size of the tumor and other patient factors like lung volumes or other things. So defining an optimal approach for all patients really is not possible.

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LAUREN BERGER:
Thank you for your question, Stephanie. We'll take the next question from the Spanish-speaking audience and a patient named Angelo asks, "Would you please address what oncologists are recommending in terms of exercise and diet during cancer treatment for NHL and CLL?"

DR. CHRISTOPHER FLOWERS:
That is a very important question. Exercise and diet are probably two of the most commonly asked questions that I receive in clinic after we complete talking about therapy and other issues related to the management of diffuse large B cell lymphoma or other lymphomas. When considering what to do, I think it is important to involve a nutritionist, sometimes to involve a physical therapist or occupational therapist, if their skills are needed, and to involve other members of the care-providing team including care providers at home, in these discussions.

In general, the principal recommendations for all patients would be to have regularly balanced diet and if that diet is not regularly balanced, to include supplements like nutritional vitamins, using a single multivitamin. And usually a multivitamin without iron. The reason for not having iron in the multivitamin is if patients need to have blood transfusions, those blood transfusions will provide a substantial course of iron and too much iron might come from additional supplementation.

For exercise I generally recommend 15 minutes to 30 minutes of walking a day with a goal of trying to achieve 30 minutes of walking, which can be divided into two or three sessions over the course of the day, and to try and do that most days of the week, which means about five days.

LAUREN BERGER:
Thank you. Thank you for your question, Angelo. Our next question is from audience in Brazil and Fernando asks, "Dr. Flowers, please talk about coping with lymphedema in legs."

DR. CHRISTOPHER FLOWERS:
That's a good question. Dealing with lymphedema can be a very challenging problem, both in the arms and the legs, which are the two most common places where it occurs. Lymphedema may occur for several reasons, one of which can be large lymph nodes that are compressing the lymphatics and causing backup of lymph or other fluid into the legs. When that occurs, and when it occurs because of large lymph nodes, the best way to address it is to try and shrink the lymph nodes, which usually involves therapy. Lymphedema can also occur for other reasons in addition and those need to be addressed individually. For all types of lymphedema it's usually appropriate to perform elevation of the legs, to keep them up higher than the heart at some portion of the day to allow drainage, and to consider the use of compression stockings to help to alleviate some of the lymphedema symptoms.

LAUREN BERGER:
Thank you. Thank you for the question. And we'll take the next question from our web audience. Helen asks, "Can you talk about the difference between virus treatments being done at Penn and CAL-101 and who benefits from each?"

DR. CHRISTOPHER FLOWERS:
That's a very good question. So the group of therapies that have been developed by the group at Penn are focused on using genetic therapies and using the virus to introduce targeted gene therapies for particular patient groups. Genetic therapies have been developed by that group and by a number of other groups that are helpful to some patients on clinical trials, but these are very early phase clinical trials and have not been broadly tested. For many patients it is challenging to have the virus introduce the genes that are needed in order to help to overcome the disease, but I think these are important trials to participate in. As of yet, these trials are so early that it is difficult to quantify a benefit from them.

Likewise, CAL-101 and many other kinds of therapies that are targeted therapies, targeted at particular pathways within the lymphoma or CLL cells, are treatments that are still relatively early in their phase. These are kinds of treatments that are developed by pharmaceutical companies and treatments that are broadly available across a number of sites where those sites have agreed to participate, either in giving the agent alone or the agent with other therapy. The expected responses in these trials likewise are relatively early on, particularly in Phase I clinical trials. Those agents or combinations that have moved on to Phase II and Phase III clinical trials, we have a limited amount, but somewhat more information about their expected responses, but they still are quite early in their development.

In predicting the response to CAL-101 for any individual, it is very difficult to predict because it depends on a number of clinical factors, including those that I highlighted as better or worse prognostic factors, among other factors.

In general the responses to CAL-101 and other agents of this category have shown quite a bit of promise early on with response rates as high in the 30s to 40 and maybe even 50% range, but it is really too early to be able to try and extend the discussion of those responses in early clinical trials to how they will work for other patients in the future.

LAUREN BERGER:
Thank you for your question, Helen. We'll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Larry in California.

LARRY:
Yes, hello. I wanted to know, Doctor, are there any trials being done on the supplement called green tea, the ECGC amount, and what amounts are needed to reduce CLL effects?

DR. CHRISTOPHER FLOWERS:
The question relates to the use of green tea in CLL. Green tea is something, or green tea extract in particular – green tea by itself would likely have limited or no impact on CLL if it's just purchased through the store – but green tea extract is a compound that has been explored in a number of trials for a number of cancers, most notably for head and neck cancer, and also for CLL. The group at the Mayo Clinic has been the lead investigating group for green tea extract and some of those clinical trials are now hopefully moving forward into broader use. But it's still also very early on in their development.

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LAUREN BERGER:
Thank you for your question, Larry. We'll take the next question from a patient in the Spanish-speaking audience and Carolina asks, "Is there a correlation between polycythemia and CLL or NHL?"

DR. CHRISTOPHER FLOWERS:
That's a very good question. So there are correlations between a number of hematologic malignancies and these may occur through common pathways or common susceptibility to disease involving either the lymph nodes or the bone marrow or early precursor cells.

For CLL and polycythemia vera, there is not really a known or directed pathway, but this is one of those potential malignancies that can occur in the same patient. But those are very uncommon and very rare.

LAUREN BERGER:
Thank you for your question, Carolina. We'll take the next question from the web audience and Mike asks, "Does progression of CLL increase as the patient ages?"

DR. CHRISTOPHER FLOWERS:
So the question relates to the progression of CLL and the age of the patient. Those things are correlated or related in that patients can have their CLL continue to grow or increase in size in their lymph nodes or in the involvement in bone marrow as they live longer with the disease. And so at any age, as someone lives with the disease, it can increase in the amount of disease if left untreated. And with treatment can sometimes relapse in ways where it becomes more aggressive. So those are related in that way.

There is an association between age and the likelihood of developing CLL and CLL does increase in likelihood as individuals age.

LAUREN BERGER:
Thank you for your question, Mike. We'll take the next question from our Portuguese-speaking audience in Brazil and the question is from John who asks, "Will a bad tooth infection affect your lymph nodes?"

DR. CHRISTOPHER FLOWERS:
So a tooth infection or any kind of infection can increase the size of lymph nodes. So the normal function of lymph nodes is to stimulate cells in the immune system or lymphoid cells to go out and fight infection. And with that you can have an increase in size of the lymph nodes. So a bad tooth infection or infection at any other site can cause an increase in the local lymph nodes to that site.

LAUREN BERGER:
Thank you for your question, John. We'll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Martin in Missouri.

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MARTIN:
Hi. I'm currently diagnosed with NHL DLBCL. I've relapsed prior to my 100-day autologous transfer, current treatment underway is methotrexate with cytarabine with the goal of reaching another transplant opportunity from my exact match brother donor. And I was interested in the piece that you were talking about, the signaling pathway receptor trials, the slide reference is SYK, BTK and P13IK. And I didn't know if all three of those are specific to DLBCL or any are better, or if they're all three different approaches for receptor trials. And then I'm trying to also better understand for DLBCL what's available out there as far as trials and what do the phases mean.

DR. CHRISTOPHER FLOWERS:
All great questions. I'll divide your question into a number of questions.

MARTIN:
And I can break them down and repeat them if you'd like.

DR. CHRISTOPHER FLOWERS:
I mentioned in the discussion of diffuse large B cell lymphoma that the common and optimal treatment approach for patients with newly diagnosed diffuse large B cell lymphoma is the combination of rituximab and CHOP therapy. However, rituximab and CHOP does not cure everyone with diffuse large B cell lymphoma. At relapse the standard approach for patients who are young enough and healthy enough would be to pursue more chemotherapy and then to follow that with autologous stem cell transplantation. In years gone by, when CHOP therapy was commonly the most used therapy in the up-front setting, we have said that autologous stem cell transplant with high dose therapy can cure up to 50% of individuals who have relapsed disease. Recent data suggests that that may not be quite as true since we are now curing more patients with R-CHOP therapy, but autologous stem cell transplant is still the preferred approach and has meaningful outcomes for many patients who've relapsed, even after R-CHOP.

However, even autologous stem cell transplant with high dose therapy does not cure everyone. And there are a number of other options for patients with diffuse large B cell lymphoma who have relapses after an autologous transplant.

Clinical trials I think are extremely important to consider for this particular patient population and there are a number of agents, including some of those that I highlighted. The PI3 kinase inhibitor, CAL-101, has been tested for patients with relapsed diffuse large B cell lymphoma. The Bruton's tyrosine kinase inhibitor or BTK inhibitor ibrutinib or PCI-32765 has been tested in this population and has ongoing trials there as well. And SYK inhibition with a drug called fostamatinib has ongoing trials and an active and open enrolling trial that is going on, and a trial that we actually have at Emory. And that looks to be a promising compound for patients with diffuse large B cell lymphoma, although it is still in the early portions of the trial.

Another drug, lenalidomide or Revlimid®, appears to be active and there is a large randomized trial that is ongoing, looking at that for patients who have relapsed after autologous stem cell transplant or ineligible.

And there are a host of other agents that are also being looked at in exactly this setting. So I think clinical trials are very important to consider in this setting.

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DR. CHRISTOPHER FLOWERS:
Allogeneic stem cell transplantation is the only demonstrated curative option for patients with aggressive behaving lymphomas that have relapsed after autologous stem cell transplant. And the first choice for an allogeneic stem cell transplant would be from a matched related sibling.

For patients who have such a sibling, it is important to be able to achieve some response to additional therapy before going on to that allogeneic stem cell transplant and to have some control of the disease going into it, because most of those allogeneic stem cell transplants need to be performed with reduced intensity conditioning if you've already had high dose therapy with autologous stem cell transplant.

But that is an important and very meaningful option and one that is in place at a number of centers across the United States.

Part of the other question related to the use of Phase I clinical trials or phases of clinical trials, in clinical trials in general exist in three major phases. Phase I is really the first testing agent for patients with lymphoma and that's where we're testing to try and identify the right dose of drug that can be safely given. So the goal of the trial is not necessarily to produce responses for patients, but to try and identify the right dose. However, for agents that appear promising and for patients for whom other treatment options are not available, these are sometimes agents that can provide meaningful benefit. Phase II clinical trials are used for agents that have already passed through the Phase I testing, where we're testing to determine whether or not this drug produces a meaningful response. And those are agents that – or those are trials that can help us to know how well patients respond. And then Phase III clinical trials are trials where we know how well patients respond to some degree and we know what the safety of the drug is, and we are comparing that approach to another more standard approach, to determine whether the newer approach is better. And so for patients with relapsed diffuse large B cell lymphoma in specific, there are a number of agents that are at all of those phases.

The agents that I mentioned are ones that are being tested individually and separate from each other, although I presented them as part of a pathway to show that they are connected in terms of the pathways that they hit within the lymphoma.

LAUREN BERGER:
Thank you so much for your question, Martin. We'll take a question from the web from Cory who asks, "I have read that years after treatment for leukemia or lymphoma, a person is at high risk for developing the other cancer, why is this?"

DR. CHRISTOPHER FLOWERS:
That's an excellent question. So there are some relationships between leukemias and lymphomas in that way. One of the relationships is a process of what's called transformation. So individuals who have low grade lymphomas, like follicular lymphoma, or other low grade processes like chronic lymphocytic leukemia or small lymphocytic lymphoma, have a risk of transformation into a more aggressive lymphoma, like diffuse large B cell lymphoma.

In general, in series that have looked at this, that risk is somewhere in the range of 2% to maybe as high as 5% per year. Meaning that that is a risk that exists and can continue over time. There may be therapies or

DR. CHRISTOPHER FLOWERS:
certain therapies that are changing that risk and additional research is necessary to determine the impact of newer treatments on that risk and some of that research is ongoing.

The other connection between lymphomas and leukemias is that either the lymphoma itself or the treatment from the lymphoma may predispose individuals to developing a secondary process or a secondary problem with the bone marrow, like myelodysplastic syndrome or myelodysplastic syndrome that develops into acute myelogenous leukemia. So a different kind of leukemia process, but a different kind of leukemia that arises either related to the disease itself, the lymphoma, or from the treatments for the lymphoma.

Slide 47: LLS Resources

LAUREN BERGER:
Thank you, Cory, for your question. And thank you all for all of your questions. We hope that many of your questions were answered and that the information will assist you and your family in your next steps. If we were not able to get to your questions, please call The Leukemia & Lymphoma Society's Information Specialists toll-free at 800-955-4572. Or you can reach us by email at infocenter@LLS.org. Our specialists can provide you with information about NHL and CLL research and clinical trials.

Please help me thank Dr. Flowers. We're so grateful that you have volunteered your time with us today.

On behalf of The Leukemia & Lymphoma Society, Abrale, Alianza Latina, Dr. Flowers and I would like to thank you for sharing your time with us today. Good-bye and we wish you well.

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