

Update on Aggressive Non-Hodgkin's Lymphoma (NHL): Diagnosis and Treatment

February 24, 2016

Speaker: David C. Fisher, MD



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Slide 1. Welcome & Introductions

OPERATOR:

Greetings, and welcome to the *Update on Aggressive Non-Hodgkin's Lymphoma: Diagnosis and Treatment* telephone and web education program.

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

LIZETTE FIGUEROA-RIVERA:

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

Special thanks to Dr. David Fisher for sharing his time and expertise with us today.

Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's Executive Director of Education & Integration, who will share a few words, Karen DeMairo. Karen, please go ahead.

KAREN DeMAIRO:

Thank you, Lizette. I'd like to add my welcome to the patients, caregivers, and health care 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. To date, we have invested over \$1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program demonstrates, we are the leading source of free blood cancer information, education, and support, and we touch patients in their communities through our 56 chapters across the United States. 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 they have access to quality, affordable, and coordinated care.

We're fortunate to have today as our presenter Dr. David Fisher, one of the nation's leading experts in lymphoma. 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 non-Hodgkin lymphoma. Thank you all, and now I'll turn the program back to Lizette.

LIZETTE FIGUEROA-RIVERA:

Thank you, Karen. We would like to acknowledge and thank Genentech and Biogen, Pharmacyclics and Janssen Biotech, and The Leukemia & Lymphoma Society for support of this program.

Slide 2. Update on Aggressive Non-Hodgkin Lymphoma (NHL): Diagnosis and Treatment

LIZETTE FIGUEROA-RIVERA:

I am now pleased to introduce Dr. David Fisher from the Dana-Farber Cancer Institute in Boston, Massachusetts. Dr. Fisher, I am privileged to turn this program over to you.

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DR. DAVID C. FISHER:

Thank you very much, and welcome to everybody. We're going to be talking about aggressive non-Hodgkin's lymphomas today, particularly large cell lymphoma, and we'll talk about mantle cell non-Hodgkin's lymphoma. We won't be talking about indolent lymphomas only because that's not the focus today. We can talk a little bit about transformed lymphomas.

Slide 3. Disclosure

As far as disclosures, I have been a consultant for Genetics Institute and Celgene.

Slide 4. An overview and management of high grade lymphoma

We'll get started today with an overview.

Slide 5. Agenda

I'll start with some basic classification and descriptions of lymphomas, talk about some of the newer subgroupings and some things that we're learning more recently about these diseases, and maybe some new approaches for them.

Slide 6. Classification of lymphoma

Lymphomas, as you know, they're malignancies of normal lymphoid cells. About 85% come from B lymphocytes, and about 15% from T lymphocytes. The majority, again, coming from B lymphocytes, will be the focus of our discussion.

There are many classification systems over the years. Currently, there are two that are commonly used: the WHO classification and the REAL, the Revised European-American Lymphoma classification systems. So we'll talk about that.

And we'll talk about some of the precursor, a number of precursor cells for these diseases, and a note here that, of course, aggressive lymphomas include Hodgkin's lymphoma, though I won't talk as much about that, though we can answer questions about those later.

Slide 7. B-cell maturation

So this is just a schematic of how B-cells mature in the normal lymph gland. So the big oval is how -- a big lymph gland that's there, and we have to the left, a naïve young B-cell. Those are the ones that give rise to mantle cell lymphoma cells.

And as they get activated by an antigen-presenting cell, they become active in the follicle. There's a center to it. There's the germinal center, and that gives rise to many of the lymphomas, including follicular lymphoma and diffuse large B-cell lymphoma.

Outside of that is the marginal zone, where these cells can give rise to the marginal zone lymphomas. And then these lymphocytes can become plasmablasts and plasma cells and go on to produce antibody, which is the goal of a normal B lymphocyte.

Most of these chances where they come into becoming malignant cells occur in the germinal center, and so we'll be talking about particularly the diffuse large B-cell lymphoma and the two subtypes that have been isolated genetically through phenotypes: both the germinal center type and the activated B-cell type.

Slide 8. Pathogenesis of B-cell lymphomas

DR. DAVID C. FISHER:

Again, this is the pathogenesis of B-cell lymphomas. You can see the different types as they evolve from the germinal center and their normal counterparts. And also listed here are many of the genes that are activated and are part of each type of lymphomas, including the Burkitt lymphomas, the follicular lymphomas, germinal center B-cell large cell lymphomas, and activated B-cell large cell lymphomas. And we'll talk about some of these genes and how they play a role in these diseases.

Slide 9. Non-Hodgkin's lymphoma

So non-Hodgkin's lymphoma is the most common blood cancer, but they're becoming more and more common each year. The incidence has more than doubled in the past 25 to 30 years in the developed world, including the United States. A cause for that is not entirely clear.

We now have about 72,000 cases of non-Hodgkin's lymphoma per year in the United States and about 9,000 cases of Hodgkin's lymphoma.

The difference between Hodgkin's lymphoma and non-Hodgkin's lymphoma is really historical. Dr. Hodgkin described the first lymphomas about 200 years ago, and those are the ones that bear his name of Hodgkin's lymphoma. The ones he didn't describe we call non-Hodgkin's lymphoma, and they're now the bulk of lymphomas.

It's the fifth most common cause of cancer death, even though we treat these diseases generally fairly effectively, particularly compared to some other types of cancers. But it's the second fastest growing in terms of mortality just because the incidence is rising, whereas other cancers, the incidences are starting to decline with lower smoking rates and other causes of the solid tumors.

As I mentioned, the majority are B-cell origin, about 85%. The rest are T-cell with an occasional natural killer cell type.

Slide 10. Presentation

So how do patients come to be found? And when I mention to patients that the incidence is increasing, sometimes they wonder, is it just because we have better screening tests, or we're picking it up better? Well, there aren't really screening tests for lymphoma, so I think that people are being diagnosed the same way that they were 30 years ago.

Two-thirds present with lymph node enlargement, often can be felt in the groin, the armpit, neck, collarbone area. Patients can have what we call B symptoms, which means either fever, drenching night sweats, weight loss of 10%.

These lymphomas, even though they tend to predominate within lymph glands, they can show up in sites outside of lymph nodes we call extranodal sites, including the GI tract and several different lymphomas, including mantle cell lymphoma, follicular lymphoma, and others within the skin. Again, follicular lymphoma, large cell lymphoma, marginal zone lymphoma -- a number common in that distribution.

And then the bone. Certainly, within the bone marrow, most indolent lymphomas are common within the bone marrow, and we can see large cell lymphoma, which we'll talk about today, certainly involving bony sites.

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DR. DAVID C. FISHER:

Less commonly, we can see them, although we certainly do, in the kidney, bladder, adrenal glands, lungs, breast, and the testes and within the thyroid, and rarely in the heart. But each of these organs are certainly recognized as being a site, and some of them require even some adjustment on the approach to treatment.

For example, when lymphoma involves the testes or the adrenal gland, there is -- or has been found an increased association of the disease finding its way into the spinal fluid and brain area. And since most chemotherapy doesn't penetrate these regions, they often require separate treatments such as high-dose methotrexate or chemotherapy given through a spinal tap, in other words, intrathecal chemotherapy.

It's somewhat controversial, but it's also felt that breast is a risk factor for this, as well as multiple bony sites, clearly a risk factor. So some of these presentations do affect how you might approach the disease.

Slide 11. Biopsy

So the diagnosis has to be made by getting tissue. Tissue is the issue. No meat, no treat. These are all the sayings that we have in the business. And certainly, usually it starts off with biopsying a lymph node.

And what I have a picture here is a fine needle with a line through it, because a fine needle aspirate is often utilized, but it is rare that it can make the diagnosis. You need a bigger piece of tissue to see the background and to get a good sampling of the cells and to be able to do all the tests that we do with antibodies, such as immunoperoxidase studies, and with gene studies, such as FISH and other things.

So we do like to get either an open surgical excision of a lymph node if possible if it's -- certainly if it's an internal node in the abdomen, that's the only place that it gets much more difficult. So, often, we can use CT scans to guide us with a core needle biopsy, a core being bigger than a fine needle, and get diagnoses through that means.

And certainly, these are sent to pathology. And in pathology they'll do special studies, including immunohistochemistry, which I mentioned. And what that is is looking for certain proteins on the surface of the cell with antibodies that have been made against these proteins. So this can really help identify whether a cell is a lymphocyte at all, whether it's a B lymphocyte, whether it's a T lymphocyte, and what subset of B lymphocyte it may be.

Flow cytometry is a way of looking at these cells through a -- again, looking at the proteins on the surface by one individual cell at a time. So this is done with sort of a liquid part, whereas immunohistochemistry is done more in a solid part. And these have become very important tools for diagnosing lymphomas.

Slide 12. Staging system

So this is just a slide to show the staging system. This is known as the Ann Arbor staging system. It's been around for quite some time, still very useful.

Stage 1 means that there's one area of lymph nodes on the same side of the diaphragm. Stage 2, more than one area. Stage 3, with lymph nodes above and below the diaphragm. And stage 4, with lymph nodes in an organ, such as the lung or the liver or the bone.

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You often hear about A or B. A means that the patient doesn't have any particular symptoms. B means it has the classic -- the patient may have the classic B symptoms, fever, night sweats or weight loss, being a 10% weight loss.

Slide 13. Infectious associations

So I talked about how the incidence of lymphoma has been rising over the past 25 years. We have been able to find that certain infectious organisms do have a role in the cause of some lymphomas -- still not the majority, but in some, and perhaps this list will continue to grow.

The most significant one, I think, is the idea of *Helicobacter pylori* causing a marginal zone lymphoma, also known as a mucosa-associated lymphoid tissue lymphoma, within the stomach. So a gastric MALT, mucosa-associated lymphoid tissue.

It's a very interesting story. Mucosa-associated lymphoid tissues mean that they're associated with the mucosa, lining of the lung or the eye or the GI tract, such as the stomach. And with a gastric MALT, we're talking about the stomach area.

Helicobacter pylori has been a bacterium that's been found to cause ulcers in -- certainly in stomachs but also has been associated with gastric MALT in over half of the patients that have this diagnosis.

And what we've found is that when we treat patients for *Helicobacter pylori* with antibiotics and antacids, or Prevpac, if you will -- that the *H. pylori* will often get cleared, and the lymphoma will often go into remission and can be a durable remission in the majority of patients by treating this only with antibiotics, which I think is fascinating.

For patients that do not remit, we have to go on to further therapies, usually radiation. But I think that's a very interesting finding of this bacteria playing a significant role.

Borrelia burgdorferi is the bacteria that causes Lyme disease, and at least a cousin of it in parts of Europe, particularly in Italy. It's been felt that this may cause a marginal zone lymphoma in the skin.

Campylobacter jejuni has been associated potentially with marginal zone lymphomas of the colon. And hepatitis C has been associated with an increased risk of marginal zone lymphomas, particularly in the lymph nodes, more standard type of lymph node-based lymphoma. And indeed, treatments of hepatitis C, which are very effective now, can lead to significant remissions in patients with marginal zone lymphoma and hepatitis C.

Epstein-Barr virus has been associated with several aggressive lymphomas, and particularly in older patients we see large cell lymphoma particularly of the elderly, it's called more commonly Epstein-Barr virus playing a role in that.

Epstein-Barr virus can play a role, certainly, in Burkitt lymphoma, particularly in the African variety. We see it in patients with Hodgkin's lymphoma, though we haven't been able to prove that it's a causative agent. It may be riding along for the -- as an innocent bystander. It's also been associated with plasmablastic lymphomas.

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Epstein-Barr virus, if you remember, is the virus that causes mononucleosis, and about 70% of people are actually infected with this virus in our lifetime here in the United States. And that virus will stay with us for the rest of our lives, and as we get older and our immune systems inevitably get weaker, this may play a role in causing some of the lymphomas that we see, particularly large cell lymphoma of the elderly.

In the Caribbean and in Asia, particularly in Japan, human T-cell leukemia virus 1, HTLV-1, has been associated with adult T-cell leukemia and lymphoma, and this can present in different subtypes, and we know that this seems to be playing a causative role. Though again, this is a virus that's endemic in the Caribbean and the Far East, and the majority of patients with this virus never get lymphoma. But it does seem to at least play some role in the patients that develop ATLL.

Human herpes virus 8, HHV-8, has been associated with primary effusion lymphoma, which is a very rare lymphoma, and large B-cell lymphoma associated or derived from Castleman's, a relatively rare disease.

So these are interesting findings that these viruses play a role. They're not the explanation, though, for the majority of lymphomas and their cause.

Slide 14. Risk factors

We do have other risk factors, and immune dysfunction is certainly one risk factor particular -- particularly autoimmune disease. So patients with diseases such as rheumatoid arthritis, Sjögren's, lupus, etc., these diseases where the immune system attacks the body, those patients have a higher risk of lymphoma.

Certainly, those patients are often treated with immune suppressive agents to treat the autoimmune disease and that also increases the risk, though the risk is present even regardless of those medications.

Patients who are on immune suppression, such as heart transplant, kidney transplant, lung transplant, those patients do have a high risk of lymphoma, and those with immunodeficiency diseases, particularly HIV infection, particularly in the past, when we had poor control of HIV, were at higher risk of lymphoma.

There are certain exposures that may put people at risk, certainly herbicides and pesticides we think play a significant role, as farmers have a higher incidence of lymphoma, and so do Vietnam vets exposed to Agent Orange, which is a very powerful herbicide. So these are certainly playing a role.

Prior therapy -- chemotherapy, radiation therapy -- probably causes some increased risk for patients down the line years later, and that may have to do with sort of overall immune suppressive effects, long-term effects of therapy.

And then genetics. We don't have a good answer on genetics in that we don't have an isolated gene. Now, is there a certain gene, like for breast cancer? We have BRCA1, BRCA2, and other genes. We have not isolated a specific gene that is -- might be within a family that puts people at risk for lymphoma.

We do know from studies at our institute that our patients who have lymphoma, if we look at their family at least one generation in each direction, there is an increased risk of lymphoma. It may be as much as seven times that of the general population, but keep in mind that the risk of getting lymphoma is about 1 in 40,000, so seven times that is 7 in 40,000. So even family members have a 39,993 out of 40,000 of not getting lymphoma. So we still don't have a lot of answers as to the cause of most lymphomas.

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Slide 15. Clinical behavior of non-Hodgkin's lymphoma

DR. DAVID C. FISHER:

And just to give you a breakdown, again, we're talking about the more aggressive types of lymphomas. But to separate it out from the indolent, where survival without therapy for indolent lymphomas could be years; for aggressive lymphomas, like large cell lymphoma, a month; a highly aggressive lymphoma like Burkitt's lymphoma is only weeks.

As far as response to therapy, the aggressive and highly aggressive lymphomas tend to be potentially curable with therapies. Indolent lymphoma is more difficult. And we can give examples there. A large-cell lymphoma is going to be what we'll be focusing on.

Slide 16 & Slide 17. High-grade lymphoma

So high-grade lymphomas. As I mentioned, the aggressive lymphomas -- highly aggressive, such as Burkitt's, T-cell ALL and lymphoblastic lymphoma, we're not going to focus so much on those.

Slide 18. Diffuse large B-cell lymphoma

We're going to talk more about diffuse large-cell lymphomas. This is the most common type of lymphoma, making up 25 to maybe as many as 30% of lymphomas. Median age at diagnosis is 65. A little more common in men than women, though not dramatically so. And we will focus on that.

Slide 19. Therapy for DLBCL

Therapy for large cell lymphoma. So we had no therapy until, in the 1960s, chemotherapy was started. Some of the first studies of use of chemotherapy here at Dana-Farber Cancer Institute back in the '60s. And by the '70s, we had recognized a number of drugs and started putting them in combination of drugs that had different side effects, so that you weren't piling up the same side effect with different -- with the same drug -- or different drugs.

So by the '70s, we were able to put together a combination of CHOP, a very commonly used acronym for a commonly used regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone. And that has been the basis of therapy, actually, for 40 years now in the treatment of large cell lymphoma.

In the 1980s, we tried to improve upon that with what we called second and third generations by adding other agents, changing the doses. So we compared some of these regimens in the 1990s to CHOP and found that they were no better. So over a decade's work without any improvement.

Slide 20. Rituximab – anti CD20 monoclonal antibody

But then starting in the late 1990s, a new drug came along that's being shown in the schematic here known as rituximab, which many of you have heard of. It's an antibody, a manmade antibody directed against CD20, a protein that is on the surface of B lymphocytes. And so it binds and it uses NK cells and antibody and complement-directed mechanisms to attack the -- attack and kill the cancer cells.

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Slide 21. International Prognostic Index

DR. DAVID C. FISHER:

And so the addition of Rituxan[®] to CHOP -- we now call R-CHOP -- has changed the outcome significantly for this disease. As you can see on the left, pre-Rituxan[®] survival rates depending on risk factors, five risk factors listed below that were actually isolated and described at Dana-Farber, and how survival rates varied considerably depending on those risk factors. In the Rituxan[®] era, survival rates are much better, approaching 94%, in the patients with the lowest risk factors.

Slide 22. Gene expression profiling in DLBCL

I talked about gene expression profiling before as one of the first ways that we had to sort of separate out large cell lymphoma by prognosis other than International Prognostic Index; these clinical factors that we described on the last slide.

And gene expression profiling, we were able to separate out two different subgroups. This was done at two different centers, including Dana-Farber, but with improved outcomes in those cells that came from the germinal center of the follicle within the lymph gland, and that they had a better outcome for whatever reason than patients with an activated B-cell type.

Slide 23. B-cell receptor signaling

So here's a schematic of B-cell receptor signaling showing the inside of the follicle where some of these different types are -- the germinal center and the activated B-cell type. And these -- this shows the B-cell receptor, which is on the surface, and how B-cells bind to their targets through the B-cell receptor.

That leads to turning on the B-cell to produce antibody and to potentially make extra copies of itself to fight infection. That's great when it's a normal B-cell. It's not so good when it's a malignant B-cell.

Slide 24. Novel targets in ABC DLBCL

And these show some of the important enzymes and some medications that may be able to attack these. There are some newer drugs, particularly in the slower-growing lymphomas, that attack some of these proteins, including Btk and PI3, and we have new drugs in that -- in those -- for those drug -- for those subtypes that attack those different enzymes.

There are other ways that we can attack through mTOR, NF-kappa-B and some others, and these are potential targets. A way of treating lymphomas now, I think, in a smarter way, whereas old-fashioned chemotherapy like CHOP would kill cells rather indiscriminately, it would affect cells that were actually actively growing, which is why people would lose their hair. They would have nausea because the lining of their GI tract would be affected. It would affect their blood counts, because those are produced on a regular basis.

And so chemotherapy being not so exact, we now have targets for more targeted, more specific drugs that hopefully will have fewer side effects.

So this is helping us try to look at the subtype of activated B-cell type large cell lymphoma and whether we might be able to find more specific targets to improve the outcome in this subtype.

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DR. DAVID C. FISHER:

So, for example, Revlimid is being looked at in addition to R-CHOP, lenalidomide, which is a drug that works through a number of mechanisms, one through -- one way is through NF-kappa-B, and whether that can improve outcomes in patients with ABC subtype.

There are other drugs that are being looked at, including ibrutinib, which is a bruton tyrosine kinase inhibitor that's used for CLL and other low-grade lymphomas. But the question is whether it can add to the effectiveness of R-CHOP through some of these direct mechanisms.

And so these are currently being studied. We don't have any definitive randomized trials completed and resulted yet to say that we have a better way of treating ABC subtype, but we're working on it.

Slide 25. Can we improve on RCHOP?

So is there a way that we can improve outcomes right now in patients with large cell lymphoma, and can we improve upon Rituxan® and CHOP, which is a regimen that really, as you saw, was built back in the '70s?

And one regimen that has been looked at is what we call dose-adjusted R-EPOCH, which includes many of the drugs of CHOP. It adds etoposide. Though several of the drugs are given by continuous infusion over four days, including etoposide, doxorubicin, and vincristine. And the question is whether this prolonged infusion can be more effective.

In addition, when this regimen is utilized as a dose-adjusted regimen, patients' blood counts are followed after their first cycle of chemotherapy. If they do not drop to significant levels that we consider low, such as neutropenia or ANC of less than 500, then the dose is adjusted upward by 20% each time until we do reach a significant nadir. So this is a way of giving it in different form and in a more intense dosing.

Slide 26. U.S. intergroup study

So there is a trial that is underway, and it's been completed, but we don't have the results yet, in which half the patients got standard R-CHOP, the other half dose-adjusted R-EPOCH, and we are awaiting results from this study to see whether large cell lymphoma in general may be improved with this new regimen or whether there may be a subtype that may benefit, particularly from this regimen. And so there will be correlative studies, including a gene expression profiling to see if there might be certain subtypes that benefit.

Slide 27. Ibrutinib in relapsed/refractory DLBCL

As I mentioned, we're looking at ibrutinib. As you can see, in -- by itself it has some activity on the left-hand scale, particularly against activated B-cell type more than the germinal center type.

And then on the right was a single-arm trial of R-CHOP plus ibrutinib chemotherapy looking at CR rates with complete remission rates being higher in the ABC subtype, suggesting that ibrutinib was adding something to that group. And so there is a trial underway looking at ibrutinib, R-CHOP plus or minus ibrutinib, to see if it does make a difference in a randomized fashion.

Slide 28. Definition of double hit lymphoma (DHL)

DR. DAVID C. FISHER:

More recently, we have found a significant factor in helping to predict prognosis in large cell lymphoma. In general, we treated all large cell lymphomas the same in the past, and certainly with R-CHOP chemotherapy.

We had found, though, that those that express MYC or c-MYC do have a higher risk of being resistant to chemotherapy. That's particularly true if they have in common the expression of BCL-2, more so than with BCL-6, but also with that, or if all three are expressed.

And if these are expressed particularly by what we call FISH, looking for the actual genetic marker, that these subtypes have been found to be more difficult to cure with chemotherapy.

Slide 29. DHL has poor prognosis

So this is just a slide of double-hit lymphomas showing a somewhat worse prognosis in some of the regimens that have used that have had improved outcomes, including EPOCH chemotherapy.

Slide 30. No overall survival benefit of transplant

So the question has come up, what about high-dose chemotherapy, autologous stem cell transplant and -- in first remission for these patients with double-hit? In general, that hasn't been found to be particularly effective. It seems that the difficulty is getting patients into remission.

Slide 31. Intensive chemotherapy associated with improved PFS

And so a number of centers have used more aggressive regimens, such as hyper-CVAD or dose-adjusted R-EPOCH to try to get a higher remission rate. Once you get into remission, these double-hits seem to do just as well as those that aren't double-hit. So here's just an example of several intensive chemotherapy regimens showing improved outcome in these patients with double-hit lymphomas.

Slide 32. No clear benefit to upfront transplantation

As I mentioned, doing a stem cell transplant in first remission has not shown to be a significant improvement.

Slide 33. Prognostic factors

And here are several prognostic factors showing the basic subtypes and how that can affect potential outcomes.

Slide 34. Response to initial chemotherapy predicts outcome

So as I said, the difficulty is getting patients into remission. And so for patients that do have a very good initial response to chemotherapy, even with double-hit lymphomas, their outcomes tend to be very good.

Slide 35. DA-EPOCH-R in MYC-R DLBCL

One regimen that's commonly used now is dose-adjusted R-EPOCH that I had mentioned. And so this was a study looking at it in patients with c-MYC expression. 100% had c-MYC. A good portion also had BCL-2, either by FISH or by immunohistochemistry.

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Slide 36. Progression-free survival – all patients

DR. DAVID C. FISHER:

And what the NIH found, the National Institute of Health, National Cancer Institute, that survival was very impressive compared to historical controls or historical outcomes of patients with double-hit lymphomas.

Slide 37. Over-expression of MYC and BCL-2 protein associated with inferior outcomes

So here's just another slide showing that the double expression of MYC and BCL-2 can be associated with a worse prognosis.

Slide 38. Double expresser DLBCL

And then this is a slide that just describes the idea of a double expresser versus a double hit. So patients can have extra copies of c-MYC and BCL-2 -- that means they're expressers -- as opposed to actual rearrangements causing these abnormalities that are found on cytogenetic studies, particularly by FISH.

So though a double expresser does have a little bit worse prognosis, it's not as bad as someone with a double hit.

Slide 39. GCB/ABC

And this is just a schematic showing where patients with germinal center type very commonly have BCL-2 expression, less commonly in the ABC subtype, that high MYC expression, more common in the ABC subtype, but having the BCL-2 and MYC overlap falls mostly in the germinal center subgroup, and these are the difficult double-hit lymphomas.

Slide 40. DHL/DEL lymphoma summary

So double-hit lymphomas, though I've talked a lot about them, because separating them out and treating them differently has been a significant trend over the past few years. They only make up about 10% of large cell lymphomas. Double expressers, which, as I mentioned, have a higher copy of c-MYC, but not an actual gene rearrangement by FISH, make up about 30%.

They do have a somewhat worse prognosis, though we have not yet found a better way to treat them. It's the double-hit lymphomas that really have the significant difference in prognosis.

So, as I said, no clear benefit to transplantation in first remission. The dose-adjusted R-EPOCH looked very good in that one study that we looked at, and so we're looking at new and improved ways hopefully in the future to treat these double-hit patients.

Slide 41. Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

I want to mention a subtype of large cell lymphoma known as the primary mediastinal large B-cell lymphoma. This is a type of lymphoma that makes up about 7% of all large cell lymphomas, more commonly in women, particularly in their 30s, and because it presents behind the breastbone in the mediastinum such -- that's what gives it its name. But it can compress the superior vena cava, the big blood vessel in the chest, and people may get back in -- backing up of blood in the neck and in the head area. And that's known as SVC syndrome.

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DR. DAVID C. FISHER:

About half of these patients can have involvement of the pericardium or in the pleura. It can cause hoarseness by affecting the nerve that innervates the larynx and dips down into the chest. And these symptoms are common.

Slides 42. Pathology

In the past, we were able to separate these out based on how they looked under the microscope by finding increased numbers of sclerotic areas. We know now there are certain proteins that we can look for that are more common in this subtype and help us identify the subtype when we see a young -- younger patient with mediastinal disease.

Slide 43. Possible diagnostic clues: PMBCL

As I mentioned, these patients can have disease in the pericardium and the pleura. They also can have sites outside of the chest. The most common area is actually the kidneys.

Slide 44. Clinical and pathologic distinction between NSHL and PMBCL

And it can be sometimes clinically confused with Hodgkin's disease, Hodgkin's disease being -- characteristics would be on the right, and primary mediastinal being on the left, showing some of the differences that are noted. And sometimes when a young woman presents with a mediastinal mass, it can be a little bit difficult to differentiate the two.

Slide 45. Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: Results of the Mabthera International Trial Group study

This is just an article showing that in the past we treated this entity with CHOP, and by adding Rituxan[®] we had improved outcomes, which is -- which we noticed across the board in large cell lymphoma.

Slide 46. Dose-adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma

And this is a paper looking at dose-adjusted R-EPOCH, which we had talked about earlier. And this regimen has been found to be highly effective in this subtype of lymphoma, and in many centers has become the standard for treating this subtype as opposed to Rituxan[®]-CHOP, often with radiation, which had been utilized in the past. Both approaches, very effective, but it seems that with the dose-adjusted R-EPOCH, we may be able to avoid radiotherapy.

Slide 47. Diagnosis large cell lymphoma 2015

So this is just an overall outline, a breakdown of large cell lymphoma and the subtypes, and we talked about -- mostly about large cell lymphoma. There are many different subtypes, primary mediastinal being one, but many other different types that -- we could talk another hour about each of the different types.

But we talked about the most common type being large cell lymphoma, diffuse large cell lymphoma, and the various prognostic factors, including the International Prognostic Index, gene profiling of germinal center type versus activated B-cell type, and then separating them out based on chromosomes into double expressers, but particular those that have a true gene rearrangement and MYC and BCL-2 in what we call a double-hit.

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Slide 48. What about precision medicine in DLBCL?

DR. DAVID C. FISHER:

So what about precision medicine? And this is just a schematic of some of the genes that are -- that play a role in the causation of this disease. And even though we have isolated many of them, as far as finding particularly directed therapies is something that we are working on, but is not yet a standard approach.

There is a clinical trial of a drug that targets MYD88, and we'll be looking at results from that trial.

I mentioned looking at things like ibrutinib and Revlimid and whether some of these agents may play a role in the future.

Slide 49. Evolution of trials in DLBCL

This is just sort of a slide of the evolution of trials looking at CHOP versus Rituxan®-CHOP, showing that Rituxan® was better, R-CHOP given 21 days apart versus 14 days apart, and really found that that didn't have a significant difference when you added in Rituxan®, that they had similar outcomes. So now we're looking at R-CHOP versus dose-adjusted R-EPOCH, as I mentioned.

I mentioned the use of ibrutinib, looking at that, plus or minus looking at Revlimid plus or minus other agents, including bortezomib and some others.

Slide 50. Diagnosis

So I wanted to switch now, after talking about how we're evaluating and looking at potential future for large cell lymphoma. I wanted to talk about mantle cell lymphoma. Whether mantle cell lymphoma is a true aggressive lymphoma is hard to pin down. We tend to separate lymphomas by slow-growing and fast-growing.

And mantle cell lymphoma has the characteristics of slow-growing lymphoma in that it has a tendency to continue to recur after chemotherapy. However, it tends to grow more rapidly than most slow-growing lymphomas, perhaps not as rapidly as diffuse large cell lymphoma, but still a somewhat aggressive lymphoma.

When you look at it under the microscope, there are small lymphocytes, and they can look a lot like other lymphomas, including marginal zone lymphoma and small lymphocytic lymphoma. So we look for a specific immunophenotype. We're looking for proteins. CD20 is a marker on all B-cells and is involved in most of the B-cell lymphomas. And as we mentioned, that's the target for Rituxan®.

CD10 we see in follicular lymphoma, so we wouldn't see that in mantle cell lymphoma. CD5 can be seen in small lymphocytic lymphoma and in mantle cell, so it's sometimes difficult to make that differentiation. CD23 tends to be positive in CLL and small lymphocytic lymphoma, but negative in mantle cell lymphoma.

But the clear marker of a mantle cell lymphoma is CyclinD1, which is the product of a translocation between 11 and 14 chromosomes, leading to this product with a rearrangement, as you see on this slide, there leading to the protein product CyclinD1. And CyclinD1's important in cell growth, so it makes sense that it's being overexpressed -- would it cause these cells to be more aggressive.

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Slide 51. Prognosis

DR. DAVID C. FISHER:

So there are some pathologic variants of mantle cell lymphoma, including the blastic variant. Other prognostic factors include the International Prognostic Index for mantle cell, or MIPI. There are two different versions of that, but they're similar to the International Prognostic Index we talked about for large cell lymphoma.

The other thing that's important is the mitotic index, either by a stain of what we call Ki67 or Mib-1. It tells you the percentage of cells that are actually dividing in mantle cell lymphoma. And this can lead to very different types of mantle cell lymphoma.

Blastic variance can be very high, with a mitotic index of 60 or 70%. The majority of normal mantle cell lymphomas average type have a growth rate of about 30 to 40% in the mitotic index.

For those that have a lower index, less than 20% and even less than 10%, those patients tend to have a much more indolent course and tend to really be more of an indolent lymphoma than an aggressive lymphoma and can often be approached like an indolent lymphoma, perhaps even observing patients who are asymptomatic initially and treating them at a later date.

So the Ki67 index can be very helpful, and often help us decide perhaps how to treat someone with this disease, as I mentioned, even considering observation for some.

Slide 52. First-line therapy

Therapy for mantle cell lymphoma has been evolving over the past 15 to 20 years. Initially, CHOP chemotherapy was used, as was used in most lymphomas, and found that its outcome was not as good as we would like. By adding Rituxan®, it certainly improved outcomes, and so R-CHOP was the standard and has -- though still outcomes were not as we wanted to see.

The idea then came along about using high-dose chemotherapy, as this was found to be effective in patients with recurrent large cell lymphoma. How about using it even as part of initial therapy for patients with mantle cell lymphoma? So remember, high-dose chemotherapy is to give much higher doses of chemotherapy than standard treatments, about ten times the dose of R-CHOP.

This does affect the blood counts and can wipe them out even permanently. So stem cells, which come from the bone marrow, are collected from the blood, put aside while the patient receives the high-dose therapy, flushed out, and then the stem cells are given back as a blood transfusion. And that's known as an autologous stem cell transplant.

And the European MCL Network did a study of R-CHOP plus transplant versus R-CHOP plus interferon, interferon as an agent that modulates the immune system and has activity in many lymphomas, and found a significant improvement by adding in stem cell transplant. And for younger patients, that's become a significant part of many of the approaches for our younger patients.

Slide 53. First-line therapy

So we did better. We did CHOP. We did R-CHOP. We did R-CHOP plus transplant, and then found that cytarabine is also a very helpful drug in this disease.

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DR. DAVID C. FISHER:

And hyper-CVAD was a regimen that used a CHOP-like cycle of therapy followed by a cytarabine-based cycle of therapy, and found improved outcomes by -- with this approach compared to, certainly, R-CHOP, and even better than some series with R-CHOP and transplant.

A difficulty is this regimen was developed at M.D. Anderson, and when it was tried to be utilized outside of that center, nearly 40% of patients could not tolerate the therapy due to toxicity, and that was somewhat limiting.

Slide 54. First-line therapy

So what's been done is to actually look at using an aggressive regimen like hyper-CVAD, maybe with fewer cycles to cut down on that toxicity, but then to follow with a stem cell transplant. And the question is whether that's an improvement over a full six cycles of intensive hyper-CVAD is not entirely clear.

But many centers have used aggressive chemotherapy regimens such as hyper-CVAD, and another one called the Nordic Regimen, to get patients into remission, and then follow with high-dose chemotherapy in first remission.

Slide 55. First-line therapy

So we've got hyper-CVAD with good outcomes. Other chemotherapy with stem cell transplant. Perhaps hyper-CVAD with stem cell transplant. MegaCHOP and high-dose Ara-C. This is the Nordic Regimen that I mentioned. And these are sort of the basis now for most younger patients is a CHOP-like regimen, a cytarabine-based regimen and autologous stem cell transplant.

Slide 56. First-line therapy

More recently, bendamustine was compared, along with Rituxan®, to Rituxan®-CHOP, standard Rituxan®-CHOP in patients with mantle cell lymphoma, and found to have an improved outcome and have less toxicity.

Slide 57. First-line therapy

So our center and others have started to utilize that, supplanting the CHOP-based regimen with Rituxan® and bendamustine, keeping the Rituxan®-cytarabine with three cycles of each, following with high-dose chemotherapy and autologous stem cell transplant on first remission, and having very, very good outcomes. Whether this is any better than the more intensive CHOP-like therapy utilized in hyper-CVAD or the Nordic regimen is not clear, but it certainly is another option.

Slide 58. Salvage

So for mantle cell lymphoma, what do we do if this approach turns out to be ineffective or if the disease recurs at some point in the future? There are a number of drugs that have been shown to have activity in mantle cell lymphoma. Bortezomib has been FDA-approved for mantle cell lymphoma, as well as ibrutinib, which has been used primarily in CLL, but also has good activity in mantle cell lymphoma.

Idelalisib, another B-cell activation pathway inhibitor, not specifically approved for mantle cell, but has activity, as well as lenalidomide, which is now approved for mantle cell lymphoma. Zevalin, which is

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DR. DAVID C. FISHER:

radioactive Rituxan[®]. And a new drug that should be coming out in the next few months, to be approved and onto the market, it's ABT-199, or venetoclax, looks like it has activity in mantle cell lymphoma on just the exact type. How effective needs to be further worked out.

But these are agents that are being looked at for patients that have recurrent disease, and maybe we can even -- have been looking at trying to add them to initial therapy to see if we can improve outcomes in mantle cell lymphoma further.

So that sort of wraps up discussion of large cell lymphoma and mantle cell lymphoma.

Slide 59. Question-and-Answer Session

And I think we're going to turn over to the question-and-answer session and see if I can answer any questions from the audience.

LIZETTE FIGUEROA-RIVERA:

Thank you so much, Dr. Fisher, for your clear presentation. It is now time for the question-and-answer portion of our program.

And we'll take the first question from our web audience, please. Doctor, Linda asks, "I'm newly diagnosed with diffuse large B-cell lymphoma. How probable is it that I will need a stem cell transplant?"

DR. DAVID C. FISHER:

So just to repeat the question, new diagnosis large cell lymphoma, what's the likelihood of needing a stem cell transplant? So it depends on some of the details of your particular lymphoma. So I mentioned that we can prognosticate at least roughly by the International Prognostic Index, five risk factors, age over 60, elevated LDH, stage 3 or 4 disease, poor performance status -- in other words, are you quite sick -- and is there disease outside more than one area within the lymph nodes?

So the more risk factors on that, the less likely R-CHOP is going to eradicate disease. Though still, even with patients with five risk factors, outcomes are reasonable and R-CHOP is the standard.

For patients who go through that and don't achieve a complete remission, who then receive a second line of chemotherapy and have a good response, those patients would be candidates for high-dose chemotherapy and stem cell transplant. If those patients go into remission, have their disease, come back, then, again, it's a likelihood that they would need stem cell transplant.

So, depending on how many risk factors, your likely of cure with R-CHOP alone can vary from 55% to 95%, depending on the details.

Aside from that, we talked about subtypes of germinal center and activated B-cell type. As yet, we have not really separated these as a way of having different treatments. We're looking at that, but we don't have an answer for that as yet.

What we have isolated is the difference in cytogenetics, particularly if someone has a rearrangement of the gene for MYC and for BCL-2, which means they have a double-hit, as we say -- that patient more commonly will use a more aggressive regimen, such as dose-adjusted R-EPOCH.

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DR. DAVID C. FISHER:

And so, though we have not found to be trans -- to have transplant in first remission to make a significant impact, so transplant's really utilized for patients that don't go into remission or have the disease come back in the future. So hopefully, standard therapy more than likely will lead to eradication of the disease for the patient.

LIZETTE FIGUEROA-RIVERA:

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

OPERATOR:

Thank you. Our next question comes from James. Please state your question.

JAMES:

My question is, if it were to come back again -- right now it's at 90% free, but if it were to come back, can the doctor recommend a good hospital?

DR. DAVID C. FISHER:

So the question is, if the disease does come back, large cell lymphoma, after initial therapy, where do we go from there? And the -- for younger patients who have -- who are in good health, our approach has been to use what we call salvage or second-line chemotherapy. There are a number of regimens, including RICE or R-DHAP or R-GDP and some others.

And if these show the disease is still chemotherapy-sensitive, following with high-dose chemotherapy and autologous stem cell transplant can make a significant impact on the cure rates. Certainly, the high-dose therapy is often done at a larger center, and you may be referred there from your doctor for consideration of that option. But high-dose therapy in the right setting can make a significant impact.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And the next question comes from our web audience. Brian asks, "My mantle cell lymphoma has been in remission for ten years. Any discussion on relapse treatments and current survival rates would be most appreciated. Thank you."

DR. DAVID C. FISHER:

So the question is what to do in the event of a relapse with mantle cell lymphoma. And it may, and it certainly does, have a lot to do with how the disease presented, what was the Ki67 index? We talked about the lower numbers, lower mitotic index having a more indolent disease, and patients can have longer remissions. Patients with more aggressive disease may have shorter remissions.

And certainly, if there is a short remission, you're going to approach it differently than if someone's had a long -- If someone's been in remission for a number of years, you can sometimes even go back to the initial therapy they had or to a new therapy, and hope again for another long remission.

Treatment options include standard therapy, such as Rituxan® and bendamustine, Rituxan® and CHOP, and some of the newer agents that have been approved and found to be effective in mantle cell lymphoma, including bortezomib, which is often used in a regimen with Rituxan®, perhaps with **DR.**

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DAVID C. FISHER:

Decadron®. Lenalidomide, or Revlimid®, has been approved and has activity in mantle cell lymphoma. And ibrutinib, a new oral agent, has been shown to be effective.

Certainly, if someone has a relatively short remission, only a year or two, then we have to think about treating the disease more aggressively. We may want to consider even options such as allogeneic or donor bone marrow transplant. So there are a number of options out there that need to be tailored to the patient.

LIZETTE FIGUEROA-RIVERA:

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

OPERATOR:

Thank you. Our next question comes from Lori from Florida. Please state your question.

LORI:

Yes, hi. My mother was diagnosed with stage 1 non-germinal large B-cell lymphoma in her breast, which I understand is a more rare occurrence. My question is, is the treatment regimen the same versus having it occur in another place in her body? And to follow up on that, are the cure rates the same for someone who has it in their breast versus somewhere else?

DR. DAVID C. FISHER:

So the question is, does the location of the presentation of the lymphoma change outcomes for individuals? Certainly we talked about at the beginning how disease can present outside a lymph node to a number of organs: adrenal glands, testes, breast, bone, lung and others.

And so in general, even though these may be higher-risk sites, we still tend to use the same chemotherapy, usually R-CHOP chemotherapy. The exception would be if it is MYC rearranged and BCL-2 rearranged, with a double-hit. We'll often think about escalating to dose-adjusted R-EPOCH, whether it be localized to an organ, or whether it be a standard lymph node-derived lymphoma.

The one difference is that there are certain sites outside of lymph nodes that do seem to carry with them a higher risk of the disease finding its way into the spinal fluid and brain. These do include the testes, breast, adrenal gland, and multiple bony sites.

So these patients, we do recommend that they get a form of prophylaxis or preventive treatment for the central nervous system. That can be done either with spinal tap chemotherapy or by giving a drug, methotrexate, which can be given at very high doses that gets into the spinal fluid, though it does require that the drug be cleared with sodium bicarbonate, a vitamin known as leucovorin, and this -- and a lot of IV fluids that usually requires a two-day hospital stay while you monitor the clearance of the drug based on blood levels.

So it may -- Presentation of sites more commonly affects what you may add to CHOP as opposed to actually changing R-CHOP.

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LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. We'll take the next question from the web audience. Nadine and Julie are both asking about transformed lymphomas. Nadine is asking, "What percentage of indolent or slow-growing NHLs turn aggressive?"

DR. DAVID C. FISHER:

So the question is about low-grade lymphomas and their possibility of transforming into large cell lymphoma, which has been our focus today. So indolent lymphomas do have the risk where a -- usually a single clone or a single site will somehow, because of unstable DNA, develop a new change in their DNA that makes them become a more aggressive type of lymphoma, most commonly diffuse large B-cell type.

If that's the case, we do have to approach the disease like it's a large B-cell type. The risk of that for most patients with an indolent lymphoma is about a 5% risk per year. So relatively low, but not something to be ignored. So if someone develops a rapidly growing lymph node with a low-grade lymphoma that needs to be looked at and biopsied.

As far as outcomes, we find that patients that do transform to large cell lymphoma, that cure rates of the large cell with R-CHOP are a little bit lower than patients that start off just with large cell lymphoma and no antecedent low-grade lymphoma.

That's particularly true if someone's had prior chemotherapy for their slow-growing lymphoma, the idea being that these cells have survived other chemotherapies and so therefore have some increased risk of -- an inherent risk of resistance to chemotherapy.

So if a patient's had prior therapies and they're younger and they have a good response to chemotherapy, we may consider high-dose chemotherapy and autologous stem cell transplant in first remission for those patients that have prior therapy for their low-grade lymphoma prior to their transformation.

LIZETTE FIGUEROA-RIVERA:

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

OPERATOR:

Thank you. Our next question comes from Geraldine from North Carolina. Please state your question.

GERALDINE:

Yeah. I have had Mycosis fungoides, diagnosed in 2011, and was taken off of methotrexate about five months ago, and recently went to be considered for a clinical study at Baptist Hospital Wake Forest Physicians, and I was not, though, accepted for that because I'd only been on the methotrexate.

And now I've had some blood tests which shows there's no cancer in my blood, but I've been told that I should also have a biopsy of my skin. That's how my condition was manifested all along, was through my skin.

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DR. DAVID C. FISHER:

So the question is how to approach, in this case, a cutaneous T-cell lymphoma, and I can use that as an opportunity to talk about aggressive T-cell lymphomas and the different T-cell lymphomas in general. Cutaneous T-cell lymphomas are a more indolent or slow-growing type of T-cell lymphoma, like the indolent B-cell lymphomas -- again, hard to eradicate, though a number of different treatment options. And so there's a number of potential ways of approaching that disease, including skin-directed therapies, such as radiation and light treatments.

Some of the agents used as far as chemotherapy goes are often used in the more aggressive lymphomas. So peripheral T-cell lymphoma, angioimmunoblastic T-cell lymphoma, anaplastic T-cell lymphoma. These are the more common aggressive types of T-cell lymphomas, and CHOP chemotherapy is, or has been, again, the standard for these subtypes also.

Unfortunately, overall cure rates for T-cell lymphomas, aggressive types, are not as high with CHOP chemotherapy as they are for B-cell lymphomas, partly because we don't have an antibody like Rituxan® for the T-cell one.

There is one study that suggests that a subgroup of patients with T-cell lymphomas might benefit by adding in etoposide, and so a regimen that's called CHOEP is used, C-H-O-E-P. And for younger patients, unlike the B-cell lymphomas, we'll often consider high-dose chemotherapy an autologous stem cell transplant in first remission for patients with high-risk aggressive T-cell lymphomas.

A number of agents have been found to have activity in T-cell lymphomas, including brentuximab, which is an agent that attacks CD30. And if that's expressed on the tumor, that can be helpful, and so there is a trial that's been done looking at brentuximab plus CHOP versus CHOP, and we await the outcome of that trial.

There are other agents that have been approved for T-cell lymphomas, including romidepsin and pralatrexate. These could be used both in aggressive and low-grade T-cell lymphomas. So it's a -- Certainly, the T-cell group is something that we're working on and needs further improvement.

LIZETTE FIGUEROA-RIVERA:

Thank you. And we have the next question from our web audience. Barbara asks, "Are my children more at risk to develop NHL because I have it?"

DR. DAVID C. FISHER:

We have looked at our patients, at least here at Dana-Farber, in family studies have and found that if a patient has lymphoma that at least one generation in each direction has a somewhat higher risk. The risk may be as much as seven times that of the general population.

Now, that sounds like a lot, but the chances of getting a lymphoma in the United States is about 1 in 40,000. So seven times that is 7 in 40,000, which means that any given patient's family members have a 39,993 out of 40,000 of not getting lymphoma. So though the risk may be minimally higher, it's not a significant difference.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. And thank you, Barbara, for the question. The next question please from the telephone audience.

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OPERATOR:

Yes, of course. Our next question comes from Ralph from Pennsylvania. Please state your question.

RALPH:

I have a double question, Doctor. Twenty years ago I had prostate cancer, and they removed the prostate. I was in the hospital for three days. I got out of the hospital, and I was as good as new. I was able to continue all my sports activities, and I am a former professional athlete.

However, in 2014, I contracted non-Hodgkin's, and I went under chemo treatments, and in about a year or so I was cleared of the non-Hodgkin's. However, my question is, I have severe fatigue since I've had that -- well, my chemo treatments, and I was wondering if it's the chemo treatments that caused this fatigue that I have, because I used to golf three days a week, and now I can't golf at all, and even a walk out to the mailbox is, you know, tiresome for me.

DR. DAVID C. FISHER:

Yeah, I think that this is a common complaint that patients have after chemotherapy for non-Hodgkin's lymphoma and other cancers, also. But in my lymphoma clinic, chemotherapy can certainly cause fatigue during treatment and actually can linger for some times afterwards. And the question is, if the chemotherapy's done, why is there still some ongoing fatigue?

There are certain specific potential causes. If someone gets radiation, as is common in Hodgkin's lymphoma and other types, to the chest, the thyroid can be affected. And so a low thyroid is a possibility. Certainly, patients can get low thyroid even without radiation, and so for anyone with fatigue, always make sure that their thyroid function is normal, which is simple blood testing.

Another thing that's been looked at in patients, particularly men, after chemotherapy is that they tend to -- there can be, at least in a subgroup of patients, lower testosterone levels, and that may be a chemotherapy effect. And for some patients, supplemental testosterone can be helpful. Certainly, some patients after chemotherapy may have a chronic anemia without complete recovery of their red counts. Certainly, that can add to fatigue.

The other factor that I think that is sometimes underappreciated is that for a lot of patients, when they go through chemotherapy, you know, there are often four to six months of treatment, and during that time, they may not -- and certainly they'll, for good reason, be as active as they normally are. And so I think there is a bit of deconditioning that happens during chemotherapy and that takes some time to get that back.

The other thing that plays a role is that prednisone, which is often used as part of chemotherapy, can cause weakness of muscles, particularly in the upper legs and upper arms. So that's certainly noticed, getting out of chairs and things like that, where you use the thigh muscles.

So there are certain drugs that can certainly add to that. Certainly, vincristine can cause neuropathy, and that can play a role. So there're a number of things to look at. Certainly, a lot of times we don't come up with good answers, but we do -- we try to look at some of these factors that I mentioned.

LIZETTE FIGUEROA-RIVERA:

Thank you, Doctor. The next question comes from our web audience. Ruth asks, "Do you recommend patients who have a port keep them in after treatment is completed, and for how long?"

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DR. DAVID C. FISHER:

So the question is what to do with a port. Ports are often utilized, particularly if you're using agents that are what we call vesicants, where they can cause tissue damage if they leak from the blood vessel. For example, Adriamycin, vincristine, as part of CHOP, that's -- are common vesicants.

So once you're done with therapy, what do you do with your port? So there are pros and cons to having the port in. Certainly, if you're being followed closely, if bloodwork is regular and getting bloodwork is difficult, then having a port can be useful. Most patients, though, once they complete therapy, are only followed every three months or so, and so for that, blood draws can usually be done successfully.

Well -- So I would think about getting it out after chemotherapy. People say, "Well, but, yeah, it's good to have. What if I need it? What if the disease comes back?" Well, it's not a risk-free to have the catheter in. These can develop clots. They can get infected. So there are some risk factors. So I tend to get them out once I establish someone's in a complete remission. The idea, if need be, you can always put another one back in, but for most people you won't have to.

LIZETTE FIGUEROA-RIVERA:

Thank you. And we'll take the next question from our phone audience, please.

OPERATOR:

Thank you. Our next question comes from Rosalie from Florida. Please state your question.

ROSALIE:

Yes. Good afternoon. I was diagnosed with non-Hodgkin's lymphoma back in 2014, and that was due to a bone marrow biopsy, and they found that my immunoglobulin-M was like 2,755, in that range. And they've elected to not treat this at this time. It's a B, I guess, a B-cell.

But they feel like I'm really not having enough symptoms or enough problems with it to start treatment at this time. I do have other problems, of course. I have the PMR, and I have Barrett and things along that line. They did start me on prednisone, but as you were talking with the previous person, I'm noticing a lot of muscle weakness in my legs and everything on the prednisone, and I want to cut back on that.

But I just wanted to ask the question, treatment versus non-treatment. They -- What I've read, it's just as well to not start treatment unless there are really symptoms, and it really develops into something worse. Am I right in that belief, or should I be questioning that?

DR. DAVID C. FISHER:

So the question's about a patient with a non-Hodgkin's lymphoma with an IgM paraprotein, and where does treatment and observation fit in? And so this sounds like what we call a Waldenstrom's macroglobulinemia, a subtype of lymphoplasmacytic lymphoma which is one of the indolent or slow-growing lymphomas.

And in distinction to patients with large cell lymphoma, this is an indolent lymphoma where chemotherapy does not tend to eradicate disease. So we tend to hold off on patients who are asymptomatic, save our bullets, if you will, and use them at a later date when there's a clear indication -- usually symptoms such as fatigue, weight loss, effect on blood counts, effect on protein levels in this case, perhaps lymph nodes becoming an issue.

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DR. DAVID C. FISHER:

So these are the things that guide us in treating low-grade lymphoma, whereas in aggressive lymphomas, we tend to treat patients right from the outset with a goal that we can potentially eradicate disease with aggressive lymphomas in contrast to patients with low-grade lymphomas.

LIZETTE FIGUEROA-RIVERA:

Thank you, Rosalie, for the question. And the next question comes from our web audience. Sheila asks about CAR T-cell therapy after relapse from an autotransplant. "Will this prepare patients for an allogeneic stem cell transplant?"

DR. DAVID C. FISHER:

The question is about patients with relapsed disease, particularly after autologous transplant with aggressive lymphomas, and where does CAR T-cell play a role? Where does allogeneic stem cell transplant play a role?

So CAR T-cells is a relatively new technology that originally was found to have activity in some of the slower-growing lymphomas. It is now being looked at and being used with at least some success in patients with large cell lymphoma. It's still a relatively new therapy, to really have an idea of just how much success we'll have with it.

But the idea of it is that your T-cells, your immune cells, which can fight cancers, are separated out from your blood, and they are genetically modified to be able to recognize your lymphoma, whereas previously it obviously wasn't, since there was no effect and the lymphoma was progressing.

Patients were then given chemotherapy, and their T-cells, these altered T-cells, are given back as a way of attacking these cells through an immune approach. And the real focus of that is that it's a different approach than chemotherapy, in that -- So for patients that are showing significant resistance to chemotherapy, this can be effective because it's such a different mode of attack.

The question was, "Okay, can I use this to get the disease under control and think about a donor stem cell transplant?" It certainly doesn't preclude a patient potentially having a donor stem cell transplant. The question is whether CAR T-cells can even put patients into prolonged remissions on their own, and therefore obviate the need of a donor transplant, or evaluating that and still trying to get those kind of answers. So I think that it's certainly an option to consider other therapies after CAR T-cells if need be. We've got a long way to go in understanding that disease.

We do know that patients that go through allogeneic stem cell transplant, that new immune system from a donor, it can attack the lymphoma, and it can provide a cure in some patients. But that immune system can only do so much. You can't ask it to handle someone that has a lot of lymphoma that is poorly controlled. So we do try to find ways to try to get that disease in better condition prior to that type of transplant.

LIZETTE FIGUEROA-RIVERA:

Thank you, Sheila, for that question. The next question comes from Jacqueline. She asks, "If you can please address nutrition and options for natural remedies for survivors, if possible."

Update on Aggressive Non-Hodgkin's Lymphoma (NHL): Diagnosis and Treatment

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DR. DAVID C. FISHER:

So the question is, what about nutrition and natural remedies? So it's an area, a field that I think has been poorly studied, and because of that we don't have great answers. We do know that particularly in slow-growing lymphomas -- and it may be true in fast-growing lymphomas -- that having a normal vitamin D level or taking vitamin D supplementation can be helpful. So I do advise my patients to take vitamin D.

We do know that protein is needed for cell growth and repair, so certainly diets have to include adequate protein. Often, patients will ask, "Well, if my cancer needs sugar to grow, then I shouldn't eat any sugar." Well, the problem with that is that your body will keep a level of sugar in your blood.

If you look at your blood tests, for example, normal is 80 to 120 g/dl. That -- whether you eat all protein, all fat or all sugar, your body's going to keep it in that same range, so you can't starve your cancer cell without starving yourself, unfortunately.

As far as nutraceuticals or other nutrients beyond vitamin D, it's been hard to really isolate anything that has been shown to have widespread activity. In general, I tell patients if they do want to try something just to share that with a physician to make sure there isn't any potential side effects.

For example, high doses of antioxidants may interfere with chemotherapy if taken on the day of chemotherapy or the day after. There are some herbal therapies that can affect liver function. So there's a number of things that have to be considered, and so just try to include your physician in the discourse.

LIZETTE FIGUEROA-RIVERA:

Thank you. And we have another question from the web. Goldie asks, "What is the benefit of Rituxan® maintenance?"

DR. DAVID C. FISHER:

So, you know, for a long time, particularly for slow-growing lymphomas, where patients have a strong tendency to recur, the question is, can we give some type of low-dose chemotherapy afterwards to keep the lymphoma from coming back? And the problem with most chemotherapy is that it's toxic, and that using it for a prolonged period of time has not really been an option, though Rituxan®, which is a manmade antibody, and very well tolerated, is one of the first agents that we can give over a prolonged period of time and find it to be tolerable.

So there have been a number of studies looking at giving prolonged Rituxan® after patients get their therapy, initial therapy for their lymphoma.

Most schedules have now -- this more recent year, use a schedule such as one dose every two months for up to two years. And these maintenance approaches have been looked at in aggressive lymphomas, such as large cell lymphoma, and have not been found to have an impact in the aggressive lymphomas.

In the slow-growing lymphomas, particularly for patients that have a good but only partial remission to chemotherapy, that Rituxan® maintenance can play a role at least prolonging remission, though we haven't proven it actually changes ultimate survival. So there is some role for maintenance, particularly in the slow-growing lymphomas, but we haven't really found that in the aggressive lymphomas.

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DR. DAVID C. FISHER:

For mantle cell lymphoma, after standard chemotherapy, Rituxan® has, again, shown an improvement in lengths of remission, and whether that would supplant the transplant or should be used in addition to autologous transplant has not yet been clarified. If someone's not a candidate for autologous transplant, then Rituxan® maintenance, I think, in mantle cell lymphoma, of all the aggressive lymphomas, makes the most sense.

LIZETTE FIGUEROA-RIVERA:

Thank you for the question. And the next question comes from Kristen. She asks if there's any updates in the treatment for Burkitt lymphoma.

DR. DAVID C. FISHER:

So the question's about Burkitt lymphoma. And Burkitt has been both a success and a challenge in that Burkitt lymphoma is the fastest-growing type of lymphoma, one of the fastest-growing cancers known to man. Because of that, though, it does tend to be more sensitive to chemotherapy.

And so multi-agent aggressive chemotherapy regimens such as the Magrath Regimen, hyper-CVAD, dose-adjusted R-EPOCH have been very effective in this disease. And depending on presentation, patients can have anywhere from 60 to 90% cure rates for the disease.

Have we been able to improve upon some of these regimens? Well, adding Rituxan® does seem to have some additional benefit. It's a small additional benefit, but we'll take it, in Burkitt. For patients who unfortunately do not go into remission with these aggressive regimens, patients with relapsed disease, unfortunately, have very limited options and a relatively poor prognosis. So we definitely need to work on finding better answers for patients that we can't take care of their disease with their initial therapy.

LIZETTE FIGUEROA-RIVERA:

Thank you. And the next question comes from Lee. "Can you please address the role of radiation in treatment in combination with R-CHOP compared to just R-CHOP?"

DR. DAVID C. FISHER:

So the question is, where does radiation fit in? There's a couple of certain places where we'll consider using it. In general, if someone has a single bony site, I tend to use radiation in a consolidative manner, but that's after full-dose chemotherapy. There's a German study that suggests patients with bulky disease -- certainly, over 10 cm, if there's a single site, that radiation to that single site after full-dose chemotherapy can be helpful.

Is there any situation where radiation will allow me to get less chemotherapy? And the one situation for that is for patients with stage 1 or maybe limited 2 large cell lymphoma, let's say, in their neck or their armpit or someplace like that, where studies were done looking at R-CHOP chemotherapy either eight or six cycles versus three cycles in radiation, and found the outcomes were similar. So for patients with low stage disease, radiation can potentially allow a reduced chemotherapy number of cycles.

LIZETTE FIGUEROA-RIVERA:

Thank you, Lee, for the question. And Doctor, our last question comes from Cindy. Cindy asks, "What is the current perception for length of remission to be considered for the possibility of cure?"

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DR. DAVID C. FISHER:

So for large cell lymphoma, an aggressive type of lymphoma, the majority of patients tend to recur much quicker than they do with slower-growing lymphomas. In general, the majority will recur within 18 months to two years. We've always considered getting to year five as sort of pulling out the party hats and the whistles. Certainly, patients can even have relapses beyond that, though it's very rare. So it's pretty uncommon after two years, and somewhat rare after five years.

LIZETTE FIGUEROA-RIVERA:

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

Slide 60. LLS Resources

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

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

Dr. Fisher, 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 we wish you well.

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