NHL: Update on Slow-Growing Lymphomas

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Speaker: Owen A. O'Connor, MD, PhD

LEUKEMIA & LYMPHOMA SOCIETY®
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Slide 1. Welcome & Introductions

OPERATOR:
Greetings and welcome to the *NHL: Update on Slow-Growing Lymphomas* telephone and web education program.

It is now my pleasure to introduce your moderator, Lizette Figueroa Rivera.

LIZETTE FIGUEROA RIVERA:
On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you.

Special thanks to Dr. Owen O'Connor for sharing his time and expertise with us today.

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

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

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

For more than 60 years, LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients, and I'm very pleased that today you'll be hearing about some of these current and emerging treatments for patients with slow-growing lymphomas.

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 today demonstrates, we are the leading source of free blood cancer information, education, and support, and we touch the lives of patients and their communities through our 58 chapters across the US and Canada.

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

We are very fortunate to have as our presenter today Dr. Owen O'Connor, 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 slow-growing lymphomas.

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

LIZETTE FIGUEROA RIVERA:
Thank you, Rick.

And we would like to acknowledge and thank Genentech and Biogen Idec and Gilead for support of this program.

Slide 2. NHL: Update on Slow-Growing Lymphomas

LIZETTE FIGUEROA RIVERA:
I am now pleased to introduce Dr. Owen O'Connor, professor of medicine and experimental therapeutics and director at the Center for Lymphoid Malignancies at Columbia University Medical Center in New York, New York.

I am privileged to turn this program over to you, Dr. O'Connor.

DR. OWEN O'CONNOR:
Thank you so much, Lizette, and thank you, Rick, for your kind words. I want to thank The Leukemia & Lymphoma Society for their many, many, many years of commitment. I have had a longstanding, incredibly productive relationship, both working with them and watching them as they really focus on their mission, which is to cure all patients that have blood cancers from these particular diseases.

Slide 3. Disclosure

Slide 4. The Indolent Lymphomas: An Overview

What I'm going to do today, it's a somewhat ambitious agenda for us, but what I'd like to do is walk you through what I think are some of the highlights in the field. And I'd like to start by introducing some simple concepts about the biology of the disease, answering the question, just what is lymphoma? I find a lot of patients get a little confused trying to think about cell of origin and exactly what kind of disease the lymphomas are, especially when they hear friends and colleagues battling diseases like lung cancer or breast cancer or prostate cancer, where envisioning those particular organs is somewhat easier.

The classification of lymphomas is incredibly complex and something that continues to evolve. But what I'm going to do is try to introduce you to the concepts in terms of the classification and at least trying to recognize the vast diversity of diseases that come under this rubric of lymphoma.

We'll talk about lymphoma epidemiology, pointing out that it's a rare disease, especially when we think about the subtypes. But I'm going to equally highlight the incredibly promising and exciting times that we're living in at the moment with regard to new treatments for these diseases. We'll talk about new highly targeted small molecules that are, in my opinion, not chemotherapy. These are precision-targeted small molecules that are actually hitting the roots of these diseases. And we'll try to put some of those treatment concepts into perspective. One of the ones that keeps coming up with the indolent lymphomas is what about maintenance Rituxan®, and it's a complicated issue. There's really not one simple answer. But I'm going to try to point out some of the major issues that doctors and patients alike need to consider when they talk about maintenance therapies.

Finally I'm going to talk about what I think is one of the more exciting areas in lymphoma research today and that is the emergence of an incredible armamentarium of new biological agents. And when I'm done you'll appreciate that for many of these diseases, an era of thinking about treatment without chemotherapy is in sight. And the idea of trying to modulate, manage these diseases with biologic agents is here and only going to become more sophisticated. And I'm going to end with a couple of simple principles about treatments, just to highlight how your physician thinks about these diseases, so that when they make recommendations you can put them into some understandable context.

Slide 5. Our Rapidly Moving Pace of Discovery in Lymphoma Knowledge and Treatment

DR. OWEN O'CONNOR:
As I pointed out, we recently published with a colleague of mine, Kensei Tobinai, in Clinical Cancer Research, an entire issue devoted to the changing and shifting paradigms in the care of patients with lymphoma. And I don't want you to at this moment digest each and every bullet on this slide. It's simply put there to try to highlight all of the advances that have been made both in our biological understanding of these diseases, which you can see on the top, as well as some of the therapeutic advances. And in fact, I didn't have enough space to put all the therapeutic advances on the bottom.

So on the top you see some of the major highlights in our classification of these diseases, where the emphasis has gone from simple morphological descriptors of the disease, now to a new era when we're really beginning to look at some of the genomic and genetic features of these diseases, which is really giving us new insight into defining high-risk disease versus relatively low-risk disease.

On the bottom, I just simply point to some of the new drugs that have been approved by the US FDA [Food and Drug Administration] for different kinds of lymphoma, and you can see a list of some of those agents, but this is in no way intended to be absolutely comprehensive of all the therapeutic advances made over the last decade.

Slide 6. Where Do Lymphomas Come From?

So the first question is where do lymphomas come from? And I'm not going to be addressing the question, what caused my lymphoma? What I want to do is sort of address the question, what is lymphoma and where do they come from as we think about the body and as we think about the cells in the body?

Slide 7. The Human Body is a Highly Organized Network of Interacting Systems

And to start from the literally very beginning, I think it's very important to realize that the human body is a highly organized network of interacting systems. We know that simple atoms of carbon and hydrogen and oxygen are bound together in unique ways to create what we refer to as biomolecules. Those biomolecules that make up the human body include proteins, lipids, nucleic acids, and carbohydrates. Those biomolecules are assembled in very unique ways to create the functioning centers that live within the cell, that help drive the natural metabolism and physiology of the cell. Organelles like the mitochondria, organelles like the nucleus that houses the DNA. It's a collection of these organelles that together work as its own interacting system to create a cell.

And when you think about cells in the body, it's important to recognize the vast diversity as well as the vast number of cells that make up the human body. There are over 50 trillion cells that make up the human body. And these cells, at different points in their life cycle, are dividing and dying according to their own natural rhythm. In fact, there are probably well over 100 different kinds of cells. So when we think about different kinds of cancers, it's very important to think about what organ or what kind of cell did that that cancer come from. A breast cancer cell that gives rise to a malignant cell, that travels to the liver, is still a breast cancer cell. It's not a liver cell; it's just disease that might be metastatic. And so cells are really the fundamental level at which we look at and make diagnoses of different kinds of cancer.

Slide 8. The Collection of Blood Cells is a Type of Connective Tissue

DR. OWEN O'CONNOR:
These cells are assembled into essentially four different kinds of tissues. And those tissues work together to form different organs, and interacting organs, of course, form different organ systems.

And so when we think about blood, blood in fact is a kind of tissue. It's a kind of connective tissue. And you can see that the hematopoietic system, that part of the body of those interacting tissues, is actually composed of four or five different things. The hematopoietic system includes bone marrow, the spleen, tonsils, lymph nodes, and small clusters or patches of lymphocytes that live along the gastrointestinal tract. And the fundamental role for many of the cells that live in these particular tissues is to play a role in your immune response, to help protect you from bacteria, and to provide cells that are necessary for carrying oxygen and to facilitate clotting as in the form of platelets.

Blood is considered a connective tissue because interestingly it is derived embryologically from the same tissue that gives rise to bone, muscle, and cartilage, and some people, I think jokingly, refer to blood cells and blood tissue as connective tissue because it connects the systems together. It's not a technical term; it's just an easy way to kind of think about the hematopoietic system.

Slide 9. Where Does Lymphoma Come From? – The Cell of Origin

So when we think about the different kinds of hematopoietic cells, in the bone marrow lives probably one of the most interesting cells in the entire human body, and that's the hematopoietic stem cell. The hematopoietic stem cell has the ability to produce any other cell that you need in your circulating blood, depending on your body's needs. So it can create and produce cells that can become platelets, which play a role in clotting. It can produce red blood cells that carry oxygen. And it can produce a variety of white blood cells that play a fundamental role in your immune system.

White blood cells, it turns out, come in two big flavors. We refer to them as myeloid cells, which includes eosinophils, basophils, neutrophils. Those of you that are struggling with these diseases at the moment know your doctor focuses a lot on neutrophils because these are bacteria-fighting white blood cells. And before you get any kind of chemotherapy your physician and you want to make sure that your neutrophils are at a healthy enough level to fight off infection.

The other kind of white blood cells are called lymphoid cells, and these come in three different flavors, what we call B lymphocytes, T lymphocytes, and NK cells. So lymphomas are fundamentally diseases derived from those lymphoid white blood cells. And there are lymphomas that are B lymphocyte lymphomas or B-cell lymphomas; they comprise about 85% of all lymphomas. T lymphocyte-derived lymphomas comprise about 10% to 15%. And lymphomas derived from these NK, or natural killer, cells comprise about 1% of all lymphomas.

Interestingly, there are over 70 kinds of lymphoma. And this number is actually increasing. And my guess is by the time we do this phone call again in a year or two, there are probably going to be way more than 70 kinds, as our ability to classify these diseases at a molecular level becomes more and more refined.

So the first question some of you may be asking is, wow, how do you get 70 kinds of lymphoma from one kind of cell? The B lymphocyte, for example, or the T lymphocyte, for example. And the answer is it has everything to do with the natural maturation or the natural development of those cells in the human body.

Slide 10. B- and T-Lymphocytes Naturally Undergo "Controlled" Recombination SHM, Leading to Immunoglobulin Diversity

DR. OWEN O'CONNOR:
As you can see on this graph, you can see a picture of the femur, and that's the place where those hematopoietic cells first produce different kinds of early white blood cells like B lymphocytes and T lymphocytes. In the bone marrow, if you liken this development or this ontogeny to the life cycle of a human being, you might think that in fact the earliest born cells from the bone marrow would be like children you bring home from the hospital. Over time those children become toddlers—they walk, they begin to go to kindergarten, they begin to go to high school, they go to college, they get a job, they become professionals, contributing to a highly functioning society. Well, the same paradigms are true when you think about these white blood cells and their levels of maturation.

Except when we think about the education of a B lymphocyte, the school or the place of higher education if you're a lymphocyte is actually the lymph node and a lot of those lymphoid organs. And so as that cell matures and leaves the bone marrow, it circulates around the body and it enters the lymph node. And in the lymph node it undergoes a whole variety of different kinds of genetic rearrangements. Those genetic rearrangements, if you're a lymphocyte, is an education. It's a way of teaching those white blood cells how to recognize different antigens and different infectious agents in the environment, so when the time comes that you need to fight an infection, those cells are sitting there poised and ready.

So how do we get 70 different kinds of lymphoma? We get 70 kinds of lymphoma because it depends where in the natural history of the development of those B lymphocytes the disease is derived. So if the lymphoma derives from those very early primitive blood cells in the bone marrow, we might call it acute lymphoblastic leukemia. If it happens just before those cells enter college, we might call it mantle cell lymphoma. If it happens while the cells are in college, we might call it follicular lymphoma or diffuse large B-cell lymphoma. And as those cells mature, leave college, and go on to become professionals in the immune system, we might think of it as chronic lymphocytic leukemia. Those are the professional kinds of infection fighting cells in the body.

And while this is an oversimplified representation of the process, it gives you a paradigm by which you can now think about different kinds of lymphomas and how that diversity is generated, based upon the natural ontogeny of these cells in the human body.

Slide 11. A Hierarchy of How Heterogeneity Can Be Viewed in Lymphoproliferative Malignancies

So when we think about lymphoma, and I mentioned that there are 70 kinds, that's largely predicated on looking at cells under the microscope, and I did mention that it is getting more complicated as we begin to understand the genetic basis of these diseases. So in the upper left panel where you see it says tissue cytomorphology, when you look at these diseases under the microscope, nobody in the universe can differentiate all those 70 different kinds of lymphomas by looking at that panel on the left. In fact, what they have to do is use new techniques and immunohistochemistry—maybe they're not so new—and those immunohistochemical techniques are actually antibodies that stain proteins on the surfaces of those cells. And every different kind of lymphoma has its own signature of different kinds of proteins on the cell. And what lymphoma experts are real good at doing is memorizing and understanding the relative implications of different levels of protein expression on those cells and what diseases that pattern of protein expression is associated with.

DR. OWEN O'CONNOR:
And so CD10, for example, would be characteristically expressed in patients with follicular lymphoma; BCL6 in a kind of germinal center diffuse large B-cell lymphoma. And you can see some of those patterns. This is just a representative panel.

Increasingly our understanding of different kinds of genetic or chromosomal rearrangements, using something called FISH, fluorescent in situ hybridization, or CGH, comparative genomic hybridization, allows us to actually look at how abnormal those chromosomes are in the malignant tissue relative to what we know about the normal tissue, and there are very particular genetic events that happen in certain kinds of lymphomas but not others. And those kinds of genetic events also can provide a form of signature that allows us to try to discriminate one lymphoma from the next. And, in fact, the most recent example of this has been demonstrated by a lot of groups now looking at something called gene expression profiling, where we now have the capability to look at tens of thousands of genes in these tumor cells and find out what genes are on; in this case what's red in that panel, and what genes are turned off, what's blue. And if you look at that panel, you see the gene expression array: You see red on the left and green on the bottom and to the far right green on top and red on the bottom. Believe it or not, that disease is all one disease. That's diffuse large B-cell lymphoma. But you can see that what gene expression profiling does for us is it allows us to sort of dissect that disease into distinct types. And we know that patients who have the kind of diffuse large B-cell lymphoma seen on the right, described as germinal center, generally have a slightly better prognosis than patients who have the one on the left. But now we're developing drugs that target that underlying biology. So trying to differentiate those different kinds of lymphoma is really a highly sophisticated and technical process that involves building layers of information.

Slide 12. Gene Expression: Follicular NHL

And so as if the whole story wasn't complicated enough, there is a lot more data now and a lot of interest in looking not just at the genes expressed in the tumor cell proper, but to look at the genes expressed in the soil or the microenvironment where those malignant cells live. And in fact, some work from a number of groups, including Dr. Gascoyne up in the British Columbia Cancer Agency, was among one of the first to discriminate changes in that soil or changes in that microenvironment, and he was able to demonstrate that if you had a change—he called it immune response 1—you had a slightly more favorable prognosis than patients that had immune response 2. And that response, that favorable or unfavorable prognosis in that case revolve not so much around the genetics of the tumor itself, but more around the genetics of the environment, where those cells live, meaning those kinds of normal white blood cells that are attracted to actually support the survival of the cell.

Slide 13. Clonal Expansion

And so in that context I think it's actually important to point out, what is clonal expansion and what do we mean by a malignant cell? And this gets complicated, but the idea is that if you see those three types of cells that are drawn there in gray, in pink and blue and gray and black, if you see that and you see a diversity of different kinds of cells in a microenvironment, that represents polyclonal. It's a mixture. Poly means many, and clonal means one. So it means many different types.

DR. OWEN O'CONNOR:
But a malignant process is one that allows one of those subtypes to grow out and dominate that cell population at the exclusion sometimes of those other cells. And when we think about these kinds of defects, we think of them as growth defects or survival defects. And, in fact, tumor cells have some combination of these growth and survival defects. Defects in growth can be you've got the accelerator on, the cells are growing in an uncontrolled way. Or another growth defect is the natural brakes of cell growth are broken, so the brakes don't work. So one of those two kinds of defects lend themselves to the successful proliferation of the tumor cell.

Survival defects are there, are signals that tell the cell to die in the tumor cell; those get lost. And there are signals that tell the tumor cell to actually live forever; those are signals that get enriched in tumor cells.

So fundamentally when we think of the malignant, the molecular features of any kind of cancer cell, we typically can box them into one of those four categories. And I haven't discussed in this context some of the new data in terms of immunologic features that contribute to that.

Slide 14. How Do We Classify Lymphomas?

So the question is, how do we classify lymphomas? And another way to ask that is, what kind of lymphoma do I have?

Slide 15. Organizing 70 Types of Lymphoma

So lymphoma classification is somewhat complicated, but for practical purposes, we can break all those 70 kinds of lymphomas into one of two general boxes: aggressive diseases and indolent diseases. And patients love to ask me, do I got the good one, do I got the good one? Well, the reality is all our lives would be better if we didn't have to deal with any of this. But like everything in life, there's a good and a bad.

The aggressive diseases, when we think about what's quote-unquote "good" about having an aggressive lymphoma, these diseases are potentially curable. When they relapse, they're still curable. They tend to respond very quickly to therapy. And you can be cured in as little as four to five months of therapy for those diseases. The cons of an aggressive disease, of course, is it requires some form of chemotherapy. Chemotherapy has side effects. Diseases that grow fast have a tendency to produce symptoms. And relapses, multiple relapses, can get harder and harder to manage.

The indolent lymphomas, in contrast, what are the pros? Well, a pro would be these are very slow-growing diseases and so typically they don't produce symptoms fast. Watching them can be an option. And when patients hear that they say, I don't believe you, I'm going to get three, four, five other opinions, because you're not familiar with thinking about taking such a conservative approach when it comes to managing a malignant disease. But in fact, watch and wait or watch and monitoring these diseases in a conservative fashion is a bona fide treatment strategy. It's a bona fide management strategy. Treatments are less and less relying on chemotherapy, and, now with the advent of all the biologic therapies, the treatment for these diseases is getting better I think and is getting less addicted to the chemotherapy options. And the diseases can be relatively asymptomatic, even when patients have relatively large amounts of a disease.

DR. OWEN O'CONNOR:
The cons are these are not curable diseases except in some rare examples. They may require some form of lifelong therapy. They can transform to become aggressive diseases and move over to the left side. And of course, like everything, there may be treatment-related side effects. So like everything in life, there is the good and the bad.

Slide 16. History of NHL Classification

But when we think about lymphoma classification—this is just a little schematic I drew up to share with you, how rapidly things are changing—back in the early 60s and 70s the morphologic classification of these diseases, there were only about six or seven. You either had large cells or small cells or they grew as clusters or they grew diffusely in a lymph node. Nowadays on the far right, the World Health Organization, or WHO, classification really integrates all the information about these diseases, including what do they look like under the microscope, what are their immunohistochemical features, what are their genetic features, and what are their clinical features? And as we learn more about each of those features of the diseases, we're now finding that those numbers, in terms of how we classify these diseases, are being split into more and more different subtypes of disease.

Slide 17. WHO Classification of Lymphoid Neoplasms

So this just gives you a simple listing. I don't want to go through it, but it gives you a listing of four general categories of lymphoma: those very early precursor cell lymphomas; peripheral B-cell lymphomas, peripheral T and NK cell lymphomas in blue; and—something I won't be discussing today, but we see a lot of here at Columbia—the post-transplant lymphoproliferative disorders, which emerge in patients that are getting organ transplants that are on immunosuppressive therapy.

Slide 18. WHO/REAL Classification of Lymphoma

And again, this table is just meant to be some information to help you think about or at least be familiar with how oncologists think about your disease. When they say follicular lymphoma, we think, oh, you have a CD20 positive, CD10 positive lymphoproliferative disorder that carries rearrangements for BCL2. So all of this is highly technical language. You should be familiar with how we think about some of those immunophenotypic and molecular lesions as we decipher different diseases. And this may be of value to some of you in the future, as you look at the features of your unique disease and try to see how it gets classified. But it's just to provide somewhat of a framework in terms of looking at those discrete details that we use to decipher the disease.

Slide 19. The Epidemiology of Lymphoma

Well, how do we think about the epidemiology of lymphoma?

Slide 20. Lymphoma, Like Most Cancers, is a Disease of the Elderly

And I'm only going to touch on this for a couple of minutes. But like all cancers, all cancers, lymphoma is a disease of the elderly. So you can see on this plot the younger people are, so there are pediatric cancers, they tend to be very rare, and in general kids do pretty well. But what you see as you get older,

DR. OWEN O'CONNOR:
your risk of cancer goes up for a variety of reasons, but actually when you get over that 80-year-old hump, your risk actually starts to drop a little bit. So you can see that cancer is actually a disease of aging, and there's a peak that begins to subside with time.

Slide 21. 2012 Estimated US Cancer Cases

This is some data from the National Registry, looking at the estimated number of US cases of cancer. And I put this here, and I amended some of the numbers; it's dated at 2012, but it's simply meant to highlight that when you add up the total number of prostate, breast, lung, bladder, uterine cancers—the top five—it's nearly a million cases of cancer per year. But when you look at non-Hodgkin lymphoma, for example, in men—about 38,000 cases per year—and you look at it in women—about 32,000 cases a year—so in total about 70,000 cases per year of lymphoma in men and women in the United States. And it comprises about 4% of the entire cancer burden in the population.

But in comparison, it's relatively rare, and when you superimpose what I told you about 70 kinds of lymphoma, 70,000 cases with 70 types means that in general there's about 1,000 cases of each subtype. In fact, follicular lymphoma and diffuse large B-cell lymphoma are the two most common. They account for about half of all cases of lymphoma, and the remaining 35,000 cases gets split amongst the remaining 60-something subtypes of disease.

Slide 22. Cancer Death Rates by Sex

And this looks at the good news. The good news is across all different types of malignancies, the death rate from cancer is dropping. And it's continued to drop now for many years.

Slide 23. Trends in Five-year Relative Survival

And when we look at this in the context of lymphoma on the next slide, you can see what's called the five-year relative survival. So this is actually data that needs to be updated by the Surveillance, Epidemiology and End Results Program [SEER], but it brings home the message. If you look at the five-year survival rate between 1975 and 1977, about 47% of patients were alive at five years. That went up to about 51% a couple of decades later, and now it's up to nearly 70%. So a nearly 20% increase over those decades, and I'm pretty confident that when we see the next numbers it's going to be even higher.

So this is the good news. This is how I started, by trying to introduce you to the idea that this is an exciting time with lots of very positive changes. Changes that importantly you need to know result from the billions of dollars that foundations like The Leukemia & Lymphoma Society have invested. It's changes and improvements that result directly from our improved understanding of these diseases and research.

Slide 24. New "Targeted" Treatments for Indolent Lymphoma

So next, what do we think about in terms of targeted therapies? And over the last year or so we now have two new drugs that are small molecules that have been approved for patients with indolent lymphoma. And I'm only going to touch on concepts. I'm not going to go through every little detail of the data, but I'm going to try to make you aware of these new drugs and just how they are different.

Slide 25. Monoclonal Antibodies Have Clearly Changed the Natural History of FL

DR. OWEN O'CONNOR:
But this slide actually highlights the point I just made before: that there are drugs, and in particular the monoclonal antibodies have gone a long way in changing the natural history of these diseases. So what you're looking at in orange is the natural history of patients with follicular lymphoma treated with CHOP, treated with a more complex combination chemotherapy regimen. But you could see the trend changing in dramatic ways with the addition of monoclonal antibodies, and in this case it's specifically referring to the integration of rituximab into the front-line therapy of patients with follicular lymphoma.

Slide 26. Rapidly Emerging Concepts in Pathogenesis Create New Opportunities in Treatment

So there is no question that this paradigm of integrating novel drugs, and in this case a monoclonal antibody called rituximab, has changed the natural history of the disease. We'll talk about some of the biologic therapies in a moment. But I want you to appreciate—and I don't want you to memorize this, I just want you to understand the concept—that many of the new molecules that are emerging, that I'll be talking about, like BTK-targeted ibrutinib or PI3-kinase-targeted idelalisib, these molecules have emerged from our very detailed molecular understanding of how the cell transmits signals, how it actually instructs itself to behave, and how it actually responds to signals outside the cell.

Slide 27. The B-Cell Receptor Links Many Known Dysregulated Pathways in Lymphoma

And so these are very fundamental important physiologic features of every cell in the body, but in particular lymphocytes in the body need to be sensitive to the signals from outside the cell, because they need to respond to infection. Maybe they need to increase that certain kind of B-cell lymphocyte subtype to fight a particular infection. And this simply creates a map that you can see here of all these different signaling pathways that converge on instructing the cell how to behave. And in cancer many of those pathways that lead to that unbridled growth of the cell or that survival or immortality of the cancer cell, those kinds of pathways are over-represented in cancer cells, and now we have drugs to try to nullify or mitigate some of those pathways. And on the right you can see some of those interacting networks.

Slide 28. The B-Cell Receptor Links Many Known Dysregulated Pathways

But the most important point I'm going to make is on this slide here, that you can actually see all the drugs that are emerging and have emerged that actually target these very specific pathways that are over-represented in cancer cells and pathways that actually allow the cancer cell to misbehave. So let's talk about some of those drugs.

Slide 29. Ibrutinib: First-in-class Inhibitor of Bruton's Tyrosine Kinase (BTK)

And the first one I'm going to talk about is ibrutinib. And ibrutinib is a first-in-class inhibitor of a protein called the Bruton's tyrosine kinase. This is a protein that actually adds phosphate groups on different proteins in the cell, and it is linked to something called the B-cell receptor. The B-cell receptor sits outside the lymphocyte, receives signals from outside the cell that tell it to grow.

And in cancer cells we know that that pathway is constantly turned off. In a normal cell when those lymphocytes are being instructed to grow and divide to meet a new thread in the body, when that thread

DR. OWEN O'CONNOR:
is nullified, then those signals get turned off. But in a cancer cell, those signals get left on, so they're always instructing the cell to divide. So the BTK, the Bruton's tyrosine kinase, is a protein downstream of that B-cell receptor, and it represents a new target. And the molecule ibrutinib was one of the first to potently bind to this BTK protein and inhibit it. So it no longer allows the cell to transmit those signals to grow and divide. And importantly, it's an orally administered drug; it's a well tolerated orally administered drug.

Slide 30. Patient Characteristics Phase II of PCI-32765 in MCL

So when we look at some of this data, this is data from Michael Wang at the MD Anderson Cancer Center; he was among one of the first in the country to look at this in mantle cell lymphoma, and this makes the point that he's looking at patients that had bortezomib. Bortezomib is a drug approved for patients with mantle cell lymphoma. And he showed here looking at patients that had been treated with bortezomib and patients that had not. It was 68 patients in general, and as you can see from the bottom, these patients had lots of different prior chemotherapy regimens. And in this particular case, the data in mantle cell lymphoma led to approval of ibrutinib in patients with mantle cell lymphoma. I didn't show you a lot of the data, but it also has unbelievably spectacular activity in patients with chronic lymphocytic leukemia [CLL]. And so there are now lots of studies looking at how to use ibrutinib in CLL. And what's really been interesting about a lot of these new drugs like ibrutinib and idelalisib is that they appear to overcome many of the adverse prognostic features of those diseases.

Slide 31. Approved and Anticipated Uses of Ibrutinib

So for example, in CLL, there's a kind of CLL referred to as 17p depleted. There's a very important tumor suppressor gene that lives at that location called P53. And patients that have 17p deleted CLL typically have a worse prognosis compared to patients that don't carry that genetic abnormality. But it turns out that ibrutinib works very well in this population, just like it does in patients that don't have that 17p deletion. So in fact the FDA said, well, we're going to allow you to use ibrutinib in patients with 17p deletion as part of their front-line therapy. Recently, only recently, the drug was approved in patients with Waldenstrom's macroglobulinemia, and there's now a lot of exciting data that goes back to those gene expression arrays I showed you in the beginning, where adding ibrutinib to a upfront standard of care chemotherapy regimen called R-CHOP selectively works in one of the molecular subtypes of diffuse large B-cell lymphoma called the ABC subtype, which happens to be that more challenging subtype of large cell lymphoma.

So people have seen this data. There are now randomized studies that are ongoing, but it's leading many, many people to suggest that in all likelihood that form of large cell lymphoma associated with a poor prognosis, we're going to be able to hopefully override some of the poor prognostic features and improve the cure of that disease for all patients.

Slide 32. Three PI3K Inhibitors in Clinical Development

So the other small molecule that's emerging very rapidly are what are known as the PI3-kinase inhibitors or phosphatidylinositol 3-kinase inhibitors. And this is yet another protein that links the intracellular signaling pathways or messengers to the outside of the cell. And so different extracellular or

DR. OWEN O'CONNOR:
environmental signals that impact the cell can stimulate various receptors in a way that activate the PI3-kinase. And this is another one of those really crucial and really important pivot points that actually convey messages to tell the cell to divide or not to divide. So in normal cells, that balance or that switch can be turned on and turned off, and the switch works fine. But in tumor cells, you might imagine that the switch is broken. It's always in the on position, so it's always sending the signal to divide, divide, divide.

Slide 33. Idelalisib Phase 1 Study NHL Demonstrates Marked Activity in Patients with MCL and Indolent NHL

And it turns out that the first of the PI3-kinase inhibitors to be approved by the US FDA was idelalisib. We'll just touch on some of that data. But it turns out there are now lots of different PI3-kinase inhibitors that are beginning to emerge. And this is complicated biology I won't go into, but there are many different forms of PI3-kinases, and many of these drugs have different differential effects on those forms of the PI3-kinase, which may lend themselves to work better in one scenario over the next. That's going to be ironed out over the years to come.

And this is the astounding data, first generated from the Phase I data from Brad Kahl, who works up in Wisconsin. It's somewhat older data, but it makes the very dramatic point that when you look in the Phase I study of idelalisib in patients with non-Hodgkin's lymphoma, you can see this marked activity in patients with mantle cell lymphoma and indolent lymphoma. And specifically what you're looking at here, where you see zero, that's actually looking at changes in the volume of the lymph node or the tumor volume. So any deflections above zero represent growth of the disease. Any deflections below zero represent shrinkage of the disease. We call this a waterfall plot, and it actually is a very good first blush way of trying to figure out, is this drug having activity in a small number of patients or a large number of patients or all the patients.

And what you can see here on the right side is among the 50 patients with indolent lymphoma, the overwhelming majority of patients had some shrinkage of the disease. To meet the definition for response you have to be below that yellowish line that's drawn at 50%. So all of those patients would meet a formal definition of partial or complete remission. But even if you didn't have a partial or complete remission, there's still a sizable number of people who were having shrinkage of their disease.

Slide 34. Double Refractory (Rituximab + Alkylator) iNHL

And even in patients—this is data from Ajay Gopal up at the Fred Hutch Cancer Center, and he said, well, I'm going to take even worse patients; I'm going to take patients with indolent lymphoma that have failed rituximab and failed alkylator-based chemotherapy like cyclophosphamide or bendamustine. So he's specifically focusing on patients that have been treated with our standards of care, now asking the question, what should we do next? And how would a drug like idelalisib work in this population?

And again you can see from this waterfall plot that the overwhelming majority of patients have deflections below that zero line, with a majority of patients having deflections below the 50%. So in fact 50% of patients in his study had more than 50% shrinkage of the disease; 90% of patients had some improvement in their baseline tumor burden going into the trial. So these are highly positive results.

Slide 35. Phase 1B Idelalisib in NHL: Best Overall Response

DR. OWEN O'CONNOR:
And in fact the next question you might think about is, well, with all these new drugs, can I combine them with some of the standards in the front line, and can I try to make my front-line therapy even better? And, in fact, this trial looked at combining idelalisib with Rituxan or idelalisib plus bendamustine or idelalisib plus bendamustine or Rituxan. And what you can see in the cases, essentially all the cases have deflection below the zero point line, with most of those actually being responses, suggesting that it is not only feasible to combine these drugs, but it's also highly efficacious in terms of producing very good control and shrinkage of existing disease.

Slide 36. Phase 1B Idelalisib in NHL: Overall Response Rates

This is looking at those response rates in yet another way, across those populations.

Slide 37. Approved and Anticipated Uses of Idelalisib

And so we now know that idelalisib is approved for patients with indolent lymphomas, CLL, and I have no doubt there are lots of new studies that are underway looking at how to integrate this important drug into our current armamentarium.

Both ibrutinib and idelalisib are oral drugs that are being combined with Rituxan and are relatively safe. They need to be given, and you need to be followed closely by your physician.

Slide 38. Results from the Phase 1/2a Study of Navitoclax (ABT-263) in Patients with Relapsed or Refractory Lymphoid Malignancies

I'll just touch on what I think will be the next drug likely to be approved for the treatment of these diseases, and that is a drug called ABT-199. This is some data from its precursor, its predecessor, ABT-263, a drug called navitoclax, which we worked on here at Columbia with colleagues from the National Cancer Institute. This is a drug that actually turns off that signal that instructs cancer cells to live.

Slide 39. Phase 1 Study of ABT-199: Best Percent Change from Baseline in Nodal Size by CT Scan

And this is the new data with the new revised ABT-263—this drug is called ABT-199. And again in this waterfall plot you can see activity across the broad spectrum of different types of disease. This is a drug specifically addressing that signal in tumor cells that tells them to become immortal.

Slide 40. Trying to Put Maintenance Rituximab in Perspective

Well, let's talk a little bit about maintenance Rituxan. It's an issue that comes up a lot. It is an incredibly complicated issue for this kind of forum, but I will touch on what I think are some of the issues.

Slide 41. Rationale for Maintenance Therapy in Indolent Lymphoma

When we think about maintenance Rituxan it's usually the case that most patients think they want maintenance Rituxan because they want all the benefit of continued therapy. But I will warn that it may not be as simple as saying, well, let's take maintenance Rituxan and we'll extend the benefit of the disease. There are pros and cons, like with everything in life.

DR. OWEN O'CONNOR:
So we know that maintenance therapy applied to patients in induction therapy is effective. We know that it can deepen the response and lengthen the duration of remission. And we know that it has a relatively good therapeutic index with minimal toxicity in general. But I would point out that when you look at the data or you hear about data for maintenance Rituxan, there's a lot of factors to consider in evaluating all the data. And all the data is, to be somewhat frank, some of it is confusing, but a lot of it is consistent for a singular message and that is that it prolongs the progression-free survival.

Slide 42. Factors to Consider in Evaluating the Merits of Maintenance Therapy

So when you look at the data you have to ask the question, how are they using the Rituxan? In some cases they're combining it with chemotherapy and comparing to what happens when you don't combine it with chemotherapy. Do patients have a lot of disease or a little disease? What's the endpoint you're going to look at? Are you going to look at how long patients live, overall survival, or just how long they go before they develop a relapse of the disease? Are you going to look at the Rituxan maintenance in front line when patients first get treated, or are you going to look at it in the relapsed setting? And does one strategy have more toxicity than the other? One of the toxicities we now know to be associated with Rituxan is that patients do develop very low immunoglobulins that puts them at risk for sinusitis and chronic bronchitis.

Slide 43. Understanding Terminology

So I put this here so you can come back and look at it a little bit later, but when you look at these definitions it's very important to pay attention to the detail. Because the devil in this case is in the detail. Many studies look at something called time-to-treatment failure, which looks at the time you get randomized in the study to when your disease progresses or you develop toxicity or you say, I'm done, I want to come off the trial. Versus progression-free survival, which the US FDA adopts as a surrogate endpoint for its trial, that looks at objective tumor progression. So these two endpoints are actually radically different and could give you different messages when you do those trials. And, of course, the gold standard endpoint when you look at these trials is overall survival. Do patients live longer if they get it versus if they don't get it? And the consensus with maintenance Rituxan is that the progression-free survival is longer if you get it, the time to your relapse is longer, but it's not associated with an overall survival benefit because if you don't get maintenance Rituxan and you happen to relapse, you can then get Rituxan again, which is very effective at inducing a remission.

Slide 44. Preliminary Analysis of Rituximab vs Watch and Wait in Asymptomatic FL Patients

So one of the first studies to give us this insight was one from the UK from Ardeshna et al, and he looked at three strategies of patients with asymptomatic follicular lymphoma: watch and wait, just a Rituxan induction with no maintenance, and a Rituxan induction with maintenance.

Slide 45. Preliminary Analysis of Rituximab vs Watch and Wait in Asymptomatic FL Patients

And when he presented these data you could see that the top curve is the one that does the best. Here we're looking at progression-free survival, so those patients that got maintenance Rituxan went many

DR. OWEN O'CONNOR:
years longer before they developed a relapse, compared to those that just got an induction. And if you looked at the patients that had watch and wait, you can see their progression-free survival curve was not as good.

Increasingly in the United States, more and more doctors are using Rituxan, even for patients with low-volume disease, because they see there's benefit in the progression-free survival curve. And there are still about 20% of patients that don't have relapse of their disease ten years later.

Slide 46. Rituximab Maintenance Therapy in FL: The First Study (SAKK Trial)

So one of the first trials to actually compare this in a randomized way was done by Michele Ghielmini back in early 2004 in something called the SAKK trial. And here he was looking at untreated patients or they had relapsed refractory, so a hodgepodge of patients. They got induced with rituximab and then they got randomized to either a maintenance schedule or an observation schedule. And another variable to pay attention to is among those maintenance schedules, there's a lot of different ways to give the drug and many of the studies give it in different ways.

Slide 47. Rituximab Maintenance Therapy in FL (SAKK Trial): Event Free Survival

And this is the take-home message, it's what we know. The event-free or progression-free survival in this case for those patients that got maintenance Rituxan was longer, 23 months versus 11 months. It doesn't answer the question, what if you treated all those patients with Rituxan at relapse, how would they do? I'm going to tell you about a trial that's looking at that in a moment. But this trial added some credence to the idea that at least in the maintenance setting you could prolong that progression-free survival.

Slide 48. Updated EFS in SAKK 35/98: Rituximab Maintenance vs. Observation

And now with a recent update of that data, seven years later in 2010, what's really interesting to see is that in those patients that got what's called prolonged or maintenance therapy with a follow-up of nearly ten years, 25% of patients are still in remission in eight years. And this is an observation that's leading many to say, well, even if you have low-volume disease, my bias is to give you some Rituxan to see if you can't extend that benefit.

Slide 49. Rituximab Maintenance Therapy vs Re-Treatment at Progression for Indolent NHL

And John Hainsworth and his colleagues from Tennessee looked at that question of maintenance therapy versus retreatment, asking the question that if we induce patients that are Rituxan-naive or previously treated—Rituxan-naive but previously treated with Rituxan—and you randomize them to Rituxan maintenance versus retreatment...

Slide 50. LYM-5 - Maintenance vs Retreatment After Rituximab: Hainsworth Regimen

... you can see on the next slide there's an advantage in this case for the maintenance therapy here versus those that got it on retreatment. This population was a hodgepodge of different patients, different kinds of subtypes including follicular lymphoma, small lymphocytic lymphoma, relapsed or refractory disease. But in this particular case it certainly suggests a benefit for the maintenance therapy.

Slide 51. PRIMA Study Design: High Tumor Burden

DR. OWEN O'CONNOR:
I'll just talk about one more study, and this is the study that a lot of people have been waiting for updates on, by Gilles Salles from France and his colleagues. It's called the PRIMA Study, probably one of the largest studies in follicular lymphoma. But it's looking at patients with a relatively high tumor burden that have untreated follicular lymphoma. They get some form of chemotherapy and then you notice that that chemotherapy does not have Rituxan in it, and patients that are getting Rituxan as maintenance therapy or randomized to observation. So yet a slightly different population than the kinds of patients we're talking about today, where most patients if they're getting chemotherapy are getting Rituxan added to that upfront therapy.

Slide 52. Primary Endpoint (PFS) Met at the Planned Interim Analysis

And again in this particular case, those patients that are getting maintenance Rituxan, looking at the progression-free survival, seem to have a benefit compared to patients who are not getting maintenance Rituxan.

Slide 53. Subgroup Analyses Results

When you look by different subgroups, you can see that all of the different subgroups of patients, irrespective of age or FLIPI score or chemotherapy, actually seem to have some benefit from that maintenance therapy.

Slide 54. Efficacy Across Secondary Endpoints

And again when you look at the efficacy across a variety of different endpoints, the time to next anti-lymphoma therapy or time to next chemotherapy, again there are statistically significant advantages in this PRIMA Study for patients getting maintenance Rituxan.

Slide 55. PRIMA 6-Year Follow-Up: PFS From Randomization

And recently Gilles Salles presented an update of this data that still holds true. When you're looking at progression-free survival at six years, 59% of patients have not relapsed compared to 42% in those patients that had observation.

Slide 56. PRIMA 6-Years Follow-Up: Overall Survival

And this is one of the big take-home messages that a lot of people like to focus on, which is that the survival at six years is identical in both those populations. So your time to relapse may be better, but patients aren't living—to date at least, based on the data—living longer.

Slide 57. ECOG 4402 (RESORT)

And it's this ECOG trial, the RESORT trial, that's answering this question probably in the cleanest way done to date, where patients are getting induction Rituxan and then being randomized to maintenance versus retreatment. We're still anxiously awaiting results from the RESORT study, but this is a trial that

DR. OWEN O'CONNOR:
should really answer that question about the benefit versus overall survival. It's going to take years and years and years because patients are just doing better and better with the new therapies for these diseases.

Slide 58. Maintenance Rituximab in Follicular Lymphoma Where Do We Stand?

So where do we stand? I'm going to actually move on from this to get to the last topic. I've highlighted some of the points.

Slide 59. Rapidly Emerging Novel Biological Approaches

And I just want to talk about some of the rapidly emerging biologic agents.

Slide 60. Highly Promising New Approaches

If you remember from the beginning, I talked about the expression of different proteins on the surface of lymphocytes and lymphomas. These proteins I told you can provide a signature that allows us to discriminate one lymphoma from the next. But in addition, to be informative, they're also, when targeted with the right drug, potentially can have therapeutic effects. And so I think this is one of the most promising and exciting areas in indolent lymphoma research at the moment. And that is engineering different kinds of antibodies or antibody drug conjugates to hit these proteins that are expressed on the surface of these tumor cells in a highly selective way. It doesn't mean that a drug targeting CD20 doesn't also hit normal B lymphocytes, but if you have a lot of disease you're going to get an effect on both the normal and malignant cells and typically the therapeutic index of these approaches is quite high.

Slide 61. Targeting Cell Surface Proteins

And the concept is expressed here. It's what I pointed out earlier, which is that when you look at the hematopoietic stem cell and its propensity to produce all the different kinds of white blood cells you see in the body, all those white blood cells express different kinds of proteins on the surface. You can't read it so easy; I just want you to understand that they're different. So this technology can be applied not just to lymphoma, but to myeloma. And there are now lots of drugs targeting these cell surface proteins in myeloma that are going to change, I think, the natural history of the disease. They've already been implemented in myeloid leukemia's with very interesting effects, but these engineered anti-CD20 targeted molecules have lots of different moving parts and they tend to kill the cells in a variety of different ways. And you can then engineer these antibodies for one mechanism of cellular killing over another. So there's a lot of opportunity.

Slide 62. Clusters of Differentiation Define Discrete Hematopoietic Cell Lines

This slide reinforces the point in terms of looking at some of those proteins expressed on different kinds of white blood cells, which we talked about in the beginning, and everything in a red box represents a target for which we now have a drug that hits that particular protein on the surface of that particular hematopoietic cell.

Slide 63. The Anatomy of Antibody Drug Conjugates

DR. OWEN O'CONNOR:
So let's talk a little bit about one of the more promising developments in the area and that is the development of antibody drug conjugates. And this is a field that is moving incredibly fast; it's very hard to stay on top of every detail because it's moving so fast. But you all are familiar with rituximab and its ability to target CD20. And you're familiar that sometimes when you get rituximab in the other IV in your other arm you're also getting some chemotherapy: bendamustine, CVP, R-CHOP, or CHOP-based chemotherapy.

But imagine if we could find a way to link the chemotherapy directly to the antibody. We would have a way to deliver that chemotherapy not necessarily through your vein so it hits every cell or organ in your body, but allow that chemotherapy to be directly targeted to the tumor cell proper. And that's the concept behind an antibody drug conjugate. The drug is conjugated to the antibody and delivered with better precision just to the tumor cell. That's not to say it doesn't cause other toxicities, but it does, but it's a way to try to selectively allow accumulation of the drug in the tumor cell.

And the anatomy of these antibody drug conjugates is that you need a very good antibody that hits that unique target, so that unique target could be any protein on the surface of those lymphoma cells we talked about.

The drug, in green on the far right—one of the drugs that's commonly used, monomethyl auristatin E—is actually so potent that you could not inject that drug alone into the vein of your body; it would be so toxic you would die. But when you conjugate it via this linker in yellow, you can actually now deliver that highly toxic monomethyl auristatin E directly to the tumor, where it can produce really dramatic effects on the shrinkage of that lymphoma.

Slide 64. Brentuximab Vedotin Pharmacology

That's the engineering, that's the anatomy. And one of the first drugs in lymphoma was brentuximab vedotin, and brentuximab vedotin, you can see, is an antibody that targets CD30. In the top you can see in blue, that's the monomethyl auristatin E and in brown that's the linker. So when that antibody drug conjugate binds in step one to the protein on the surface of the tumor cell, it gets internalized. Once it gets internalized that drug gets cleaved off the antibody and then poisons the cell from within, and it actually very effectively can kill that cell in a very selected way.

And so now beyond brentuximab vedotin, there are antibody drug conjugates that are hitting other targets that are expressed on different kinds of lymphoma. So CD30 is expressed in anaplastic large cell lymphoma and Hodgkin lymphoma. That's where it has been approved. But it's not universally expressed on every kind of lymphoma. So now scientists are trying to find certain targets or certain proteins expressed on a greater variety of cells.

Slide 65. CD37 Is Strongly Expressed In NHL, CLL & Not HL

CD37 is one example expressed on all forms of non-Hodgkin's lymphoma and CLL, but not expressed on Hodgkin lymphoma. And that antibody is also conjugated to monomethyl auristatin E.

Slide 66. Mechanism of Action SGN-CD19A

DR. OWEN O'CONNOR:
Craig Moskowitz has recently presented data on a drug targeting a protein on B cells, also present on those very early leukemia cells called CD19. And this uses the same technology used to make brentuximab vedotin, and it uses a novel antibody that hits this CD19 in a selective way. So it hits a different repertoire of different kinds of lymphomas and kills the cell in nearly the identical way.

Slide 67. Best % Change Per Patient in Index Lesions

And when you look at this data, this is another example of one of those waterfall plots, but this is a Phase I study. So on the far left you can see where lower doses of the drug, even lower doses of the drug, had pretty good effects. And as you increase the dose of the drug, you can see at 5 and 6, comparatively more patients seem to respond. And this seems to be occurring across all subtypes of lymphoma that express that CD19. So these drugs are expressing potent activity.

Slide 68. Pinatuzumab Vedotin (CD22-ADC) Polatuzumab Vedotin (CD79b-ADC)

Franck Morschhauser from Paris has also done it with antibody drug targets hitting CD22 and CD79B. These drugs work in similar ways.

Slide 69. ROMULUS Study Design

And Frank did an interesting study under the notion that maybe the future of managing patients with indolent lymphoma is not really thinking about how to combine Rituxan with chemo, but how we might marry different combinations of these antibody drug conjugates or antibodies to create not combination chemo, but a combination biological therapy. And so Frank actually began to do this—Franck Morschhauser began to do this—in patients with large cell lymphoma and follicular lymphoma.

Slide 70. Investigator-Assessed Best Responses in Treated Patients

And you can see across the board these patients had previously treated disease. They had pretty good response rates. You can see the median duration of response in some of these patients across the board. And he was able to convert patients that had been treated with one to the next.

Slide 71. Anti-Tumor Responses Observed By Lymphoma Subtypes and Refractoriness to Last Prior Therapy

These are the waterfall plots that I showed you before, and you can get a sense that this is really very, very good activity for these particular antibody drug conjugates. And when a patient had progressed on one, they were able to cross over and get the other with a good probability of response when converting the antibody.

Slide 72. PD-1 Blockade with Pembrolizumab in Patients with Classical Hodgkin Lymphoma after Brentuximab Failure: Phase 1B

DR. OWEN O'CONNOR:
Another antibody coming along is called the PD-1 antibody. These are probably the latest, biggest, greatest breakthroughs in the management of many kinds of cancer. Some of these PD-1 type antibodies are educating your immune system to refight the lymphoma. And their activity in melanoma, lung cancer, and Hodgkin's disease has been astounding.

And as you see, as we get smarter and smarter and smarter, understanding the immune system and trying to manipulate it, here's a waterfall plot of patients with Hodgkin's disease, and you can see essentially every patient had some downward reflection after treatment with this antibody. And these were patients that were very, very heavily treated and were patients that had seen prior brentuximab. These two antibodies, brentuximab and the PD-1s, are probably going to change the natural history of Hodgkin's disease forever.

Slide 73. Principles of Treatment – 101

So I just want to end on touching on two particular points. And these are to try to establish some principles of therapy.

Slide 74. Principles of Treatment

Sometimes patients like to say, well, why do I need so many cycles of therapy? I just want to educate, I don't want to make anybody scared, but when you think about a small tumor or any kind of malignant disease in the body, the smallest tumor you can feel with your fingers has about a billion cells; so that's a 1 with nine zeroes. That's about the smallest you can see. CAT scans and the like can probably see something like 100 million cells. But let's imagine that the LLS has created the world's best therapy for lymphoma, but like everything in life, nothing's 100%. It kills 99% of every tumor in the smallest tumor you can feel in your body.

Well, if you kill 99% of that one billion cells, you're left with 10 million cells. If you kill 99% of that 10 million cells, you're left with 100,000. You kill 99% of that 100,000, you're left with 1,000. You kill 99% of the 1,000, you're left with 10.

So the goal in different kinds of therapy is can we get you to a point where you have no cells. Well, we know we can do that because we know we can cure diseases like Hodgkin's lymphoma and large cell lymphoma. We don't know that we can cure all forms of follicular or small lymphocytic lymphoma. But you can see that with each cycle of therapy, the goal is to continue to reduce that burden of cells in the body to a point where you get to something very small that might allow your immune system to take over or might allow those diseases to become quiescent or dormant for some period of time. But I just want you to appreciate some of the mathematics in terms of what's the rationale for giving four or five or six cycles of therapy.

And you can see here, even when you have scenarios that are very optimistic, small volume and highly effective drug, that even after four cycles of therapy you'd still be left with something less than 100 cells. Hence the need for thinking about more therapy. And maybe even this gives a rationale for thinking about how we might integrate maintenance therapies to continue a pressure on those relatively small numbers of cells.

Slide 75. Effects of Treatment on Tumor Burden

DR. OWEN O'CONNOR:
So this actually demonstrates the growth of a tumor cell. And one of the important points is after you get any chemotherapy of any sort, what you see in that intermediate dark green line, the disease may shrink, but before you get back to the next cycle there's actually a little bit of regrowth. There's regrowth back to where you started and that therapy is not very good, but there's always a little bit of regrowth as you wait for the body to recover. Theoretically with a lot of the biologic agents, there may not be that need to wait so long for the body to recover, but you can begin to see that with each treatment the line goes down, there may be growth, the line goes down, there may be growth, but it's this continued treatment that actually begins to try to reduce that cell number to something incredibly small.

Slide 76. The Indolent Lymphoma's Summary

So thank you all for your patience. I'll summarize by highlighting I think maybe the obvious. These diseases, as I've conveyed, are incredibly heterogeneous. Each possesses each its own features in terms of biology, in terms of clinical behavior, and now even in terms of how we might specifically treat this disease. The era of one size fits all is slowly coming to an end, as we begin to think about these diseases in very discrete biological context and now even have the tools to potentially target different diseases, based upon the makeup of that individual's disease.

The treatment is often tailored based upon the degree of tumor burden, vital organ compromise, symptoms, and comorbidities. Lots of patients chatting in the waiting room like to say, well, why is he giving you that or why am I getting this? Oh my God, he doesn't like me, he likes you, and you're getting this. There's a lot of detail that goes into trying to figure out what's the best therapy for a patient, and a lot of those details are very technical. Some of them have to do with your health and the comorbidities that you bring into the situation, which have to be addressed in careful ways.

Chemotherapy plays a pretty important role in patients with advanced burden, but I think we're going to begin to see that in many cases using biological therapy integrated and maybe with chemo-like strategies can be very effective. And I don't doubt that in the very near futures it's going to be combination biological agents that are going to be used in the front-line treatment platform, as I focused on the end, where I think the increasing emphasis will be on those small molecules and those biologic therapies creating the upfront treatment platforms that could one day replace many of the conventional chemotherapies.

Slide 77. Thank you!

I want to thank you. This is our location in midtown Manhattan. Columbia University has some space here in midtown Manhattan, right down the block from St. Pat's, in addition to its medical center space up at 168th Street. And it's within this facility we are able to see all patients. We can give them their systemic IV therapies here, CAT scans, biopsies—essentially everything needed to manage patients with various malignancies can be done at this midtown location, right across from the beautiful Radio City Music Hall.

So thank you all for your attention.

Slide 78. Columbia Faculty

Slide 79. Question and Answer Session

LIZETTE FIGUEROA RIVERA:
Thank you so much, Dr. O'Connor, for your very clear and informative presentation.

We'll take the first question from our web audience, Doctor. Thomas asks, when is the appropriate time to get a second opinion when your lymphoma has been determined to be slow-growing or indolent and no treatment has been prescribed? Should the second opinion be deferred until some sort of treatment has been suggested?

DR. OWEN O'CONNOR:
I think it's probably—I think it depends on a lot of factors. One, it depends on the comfort level of the patient in the environment where they're getting evaluated. It depends on the comfort level of the physician evaluating that patient. As I alluded to, these are rare diseases. There's only about 13,000, 14,000 cases of follicular lymphoma, for example, per year in the United States. There are only about 15,000 medical oncologists in the United States. So if you spread it out like jam on bread, that's about each medical oncologist would see about a case a year of follicular lymphoma. So with that kind of volume it's not so easy to develop the familiarity and expertise to be able to know every scenario that might walk through the door.

I think it's probably prudent to get a second opinion—if not to verify the treatment recommendations or perspective but to also confirm the diagnosis. So everything a medical oncologist recommends is predicated on the pathologist telling them that this is what it is. And these diseases, if they're rare for medical oncologists to see, in some institutions they may be rare for pathologists to diagnose. And so you might imagine that there are some hospitals that have pathologists with relatively more expertise diagnosing the diseases and some places with less expertise diagnosing the places.

So I think it's prudent to confirm the diagnosis. There's probably across the board when you look 10% to 20% of lymphoma diagnoses get revised across the board when tissue gets reevaluated at different centers. And so while the medical oncologist's recommendations may be spot on, but you want to actually make sure that the pathology diagnosis, the pathologic diagnosis at the institution, is accurate.

The other thing to keep in mind is I've spent a lot of time talking about all the excitement with all the new therapies, and I think patients should be very open to the idea of thinking about clinical trials. And there may be clinical trials at centers that focus on these diseases that might be worth joining, either so we can learn more about the disease or we can explore new treatment options in the upfront or relapsed setting. And so while you may not need treatment with conventional therapies, there may be a new vaccine that's being developed at an institution that might be looking to ask different types of questions that might be worth your time to consider. So I think it's worthwhile getting a second opinion for a whole variety of those reasons.

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

OPERATOR:
Our first caller is Bonnie from PA. Bonnie, you may ask your question.

BONNIE:
Yes, I'd like to ask you—I have CLL and IPT, and I wanted to know if there is any supplements that help you to build your immune system. And I want to know if there's any foods that we should eat, especially to help us to build the immune system.

DR. OWEN O'CONNOR:
So probably one of the most commonly asked questions from lots of patients is, you know, are there supplements I can take and what are the nutritional, are there nutritional considerations? And most physicians that see a lot of patients with these diseases will tell you not to take supplements. Though in the case of CLL there is anecdotal evidence around green tea and some of the components of green tea that may have an effect on CLL. And there's always anecdotal effects about a whole variety of alternative therapies.

And in some cases I have patients here in New York that go see people who specialize in alternative therapies, and they say, oh, this definitely works here, take echinacea or take this combination. Patients can spend thousands of dollars a month on these types of alternative therapies. And what I always like to ask is what's the data, can you show me any data? I didn't really show you a lot of data, but I tried to give you glimpses of data. But if someone is going to recommend an alternative therapy, I don't think that you should be looking at it in a way that's different from how you might look at other conventional therapies for your disease. That if I'm going to spend several thousand dollars a month, what data do you have that's been published in peer reviewed scientific journals to support the claims that you're making. Every claim I've made has been published, it's been vetted by colleagues and peers in the academic and in the community, and it gets time-tested. People get chances to criticize the data, we present the data, and then it gets published. And if it meets a certain quality bar, it gets published in good journals.

And so the problem with a lot of the herbal remedies that people tend to sell and patients tend to be seduced by, that kind of rigorous data doesn't exist. It's not published in high-quality journals, if it's published at all. So I think that you need to approach them with caution. You need to approach them with a critical mind. And you need to ask lots of directed questions about the data that is being used to support the claims.

As for diet, I think that a healthy diet, if you're overweight, my strongest recommendation is begin to see a nutritionist to lose weight. And it may be that there are simple things in human behavior that are way more important than thinking about some of the details of certain micronutrients or macronutrients. So if you're overweight, probably the best thing you can do is lose weight. If you have uncontrolled diabetes as a result of it and that represents an important comorbidity that might limit your doctor's ability to do things in the future, lose the weight and get control of the diabetes. If you smoke, stop. Thirty percent, tomorrow, I can guarantee you, we will drop the cancer rate by 30% if cigarettes went away. Thirty percent. We spend a lot of time here looking for drugs that are going to improve people's outcomes by 10% or 20%, but the single greatest impact I can make today is to burn every cigarette in a huge pile and get people to stop smoking.

DR. OWEN O'CONNOR:
So I think when it comes to lifestyle factors, getting fit, taking care of yourself—you're in somewhat of a metaphorical battle. Be prepared for the fight that lies ahead. Be in good shape. Eating well means eating three squares a day, avoiding the junk food, eating routine fruits and vegetables. Beyond that, there really aren't randomized clinical trials to say, well, the Paleo diet has a, you know, patients do better on compared to the Atkins diet or no diet.

I think that the principles are simple. If you're not fit, get fit. If you smoke, stop. And eat three squares a day, avoiding the junk food. So kind of simple, simple recommendations are important. But physical exercise I think is key.

LIZETTE FIGUEROA RIVERA:
We'll take the next question from our web audience. Loretta asks, is radioimmunotherapy such as Zevalin® still considered a good treatment option for those with follicular lymphoma?

DR. OWEN O'CONNOR:
So I would like to thank our guest for that great question. I didn't talk about radioimmunotherapy, but I did talk about the concept at large, and the concept at large is antibody drug conjugates. And in the case of radioimmunotherapy drugs like Zevalin or Bexxar®, the drug is a radioisotope. It's yttrium or it's iodine, but those are the drugs. The drug is a radioactive molecule. And in fact, yes, radioimmunotherapy drugs are highly potent drugs for certain kinds of B-cell lymphomas. So they do have very high activity in follicular lymphoma. For patients that transform the lymphoma from low indolent disease, from indolent disease to high grade disease, it works very well. And there's some data to suggest that integrating radioimmunotherapy into various bone marrow transplant regimens, whether they be autologous or allogeneic stem cell transplant settings, can be very valuable.

There's been a lot of doctors and institutions have been a little skittish about radioimmunotherapy, and, despite the promise of the drugs, they've never really caught on for a host of reasons. And one of those reasons relates to who gives the drug at an institution. It's really not the medical oncologist, it's a nuclear medicine physician in some cases. Some of that is changing. And some of it has to do with concerns about the effects on your bone marrow and your bone marrow stem cells, because if you have disease in the marrow and you concentrate radiation in the marrow that can have profound long-term consequences on your hematopoietic stem cell.

I think the future of radioimmunotherapy is probably not going to all of a sudden get dramatically better than where it is today. Especially as these other probably safer, easier-to-give antibody drug conjugates begin to emerge. But it is still an important alternative for many patients and still a drug that we use today here in our center at Columbia.

LIZETTE FIGUEROA RIVERA:
We'll take the next question from the telephone audience, please.

OPERATOR:
The next question is from Patty from Missouri. Patty, you may ask your question.

PATTY:
Yes, Dr. O'Connor, thank you for your very impressive presentation. I wanted to know more about transformed lymphoma. I'm a ten-year survivor of R-CHOP treatment for follicular lymphoma with no relapse. And what easier methods are developing for treating indolent lymphoma transformed to aggressive?

DR. OWEN O'CONNOR:
Another great question. And I didn't touch on it a lot, but transformed lymphomas probably happen at an incidence of about 2% to 3% per year, depending upon the study you look at. So if you have follicular lymphoma or some other indolent lymphoma for ten years, you're likely to have about a 30% to 40% chance that you're going to develop histologic transformation of your disease. So the question is highlighting an important feature of the natural history of these diseases, which is that over time, since we don't cure the disease that lives in your body, it can acquire additional mutations that can lend itself to now transforming its behavior from one that's slow-growing to one that's more aggressive and fast-growing. And histologic transformation does represent one of the biggest challenges we have in managing patients with indolent lymphoma because the standard of care is still to use an anthracycline-containing regimen like CHOP—that's the H in CHOP—or some regimen like that. Now there's some good probability you can be cured of the aggressive lymphoma with the R-CHOP type chemotherapy, as it sounds like you have been cured. But when you get that R-CHOP chemotherapy you can cure the new aggressive lymphoma that's developed, but you don't cure the antecedent follicular lymphoma from which it came.

So in essence when you transform your lymphoma, you have two lymphomas: the aggressive one and the slow one. So the CHOP can cure the aggressive one, it leaves you with the indolent one. It also responds to the CHOP. But it's likely at some point in the future that you could relapse with the indolent disease. If you relapse again with the transformed lymphoma, then the answer is you have to have an autologous stem cell transplant.

So what's changed? What's new? Unfortunately, in managing transformed lymphoma, not much, though the last antibody I talked about, those PD1s, could have activity in that setting that is meaningful. The question about Zevalin and radioimmunotherapy--probably the singular most active drug for transformed lymphoma is radioimmunotherapy. So many times for those patients that are going on to transplant, there's data to suggest that integrating radioimmunotherapy into the transplant regimen can be highly effective and associated with a benefit. But I dare say that we've not made spectacular advances in finding new ways, other than using R-CHOP-based chemotherapy or other intense chemotherapy approaches, to cure histologic transformation of underlying indolent lymphoma. But while I hope things get better with less chemotherapy-addicted regimens, I think patients need to be assured that we still have highly effective and curative treatments for patients who might develop transformed lymphoma. And as it appears, you've done exceedingly well.

LIZETTE FIGUEROA RIVERA:
Thank you, Doctor. And we'll take the next question from our web audience, doctor. Michael asks, how does a doctor figure out what the order of treatment should be for each patient?

DR. OWEN O'CONNOR:
So you guys are great, asking great questions. And so, unfortunately, there's no absolute consensus on how to order the different therapies. I would say that there has been a gradual shift in the United States in terms of our thinking about how to take care of patients.

So the first thing to think about is do you even need treatment? And so how most physician's approach it is they look at you and say, well, when I look at your disease, either by CT scan or bone marrow biopsy or however, we divide you into one of two boxes: Do you have low-volume disease or high-volume disease?

If you have—and those two scenarios are relatively defined in the literature—if you do have low volume disease, you generally have two options: One is you can be watched, no therapy, or you can get single agent rituximab. If you have high-volume disease, you can get single agent Rituxan or you can get Rituxan plus some chemo. And the need for chemo is largely predicated around how aggressive and how much of a need does the physician perceive you to have to get reduction of your disease. So if you're an extremist, if you're uncomfortable, if you have evidence of kidney compromise, or if you have evidence of bone marrow compromise, well, you might be somebody with high-volume disease that's got an impact of that disease on vital organ function. We need to get control of the situation fast, we're going to give you some form of R-chemotherapy.

It used to be that the front-line therapies were some combination of R-CHOP or something called R-CVP. There are some centers that believe in just giving only R-CHOP based chemotherapy. The critics of that strategy say, well, not so fast, because the H in CHOP, as you heard me mention earlier, is the most active drug for patients that develop histologic transformation. So if you get R-CHOP as your front-line therapy for follicular lymphoma and four years later develop histologic transformation that needs aggressive chemo, you say, oops, can't use R-CHOP again, so now you need to get some form of chemo followed by a transplant. So the non-anthracycline-containing or non-doxorubicin-containing regimens include R-CVP or bendamustine.

There's been a trend in the United States over the last several years, where R-bendamustine has clearly emerged as probably the most popular commonly used front-line R-chemotherapy drug for patients needing chemotherapy that have high tumor burden disease in need of treatment. I think R-CVP has largely fallen off the radar, given the remarkable activity of R-bendamustine. And down the road I think patients look at combinations of biologics, maybe Rituxan down the road to try to maintain the disease.

An important feature is if you relapse with low-grade follicular lymphoma after having high burden states, some doctors feel, oops, you've relapsed, I've got to give you more chemotherapy. And we say, whoa, not so fast. Because under the low tumor burden strategy or low tumor burden definition, there are patients that have—can be watched and patients that might get single agent Rituxan. So if you relapse with relatively low-volume disease, we usually like to say you don't need to jump into a therapy right away.

The sequencing is a good question and if you ask ten doctors about how do you sequence therapies for patients with follicular lymphoma, you're going to get 15 different answers because there is no one consensus. And in most cases it's largely tailored to the specifics of your situation. Do you have a need for the therapy, how aggressive does the therapy need to be, what comorbidities do you bring into the situation, and how rituximab-sensitive or -refractory are you before we continue recommending more Rituxan? And again, one of the great things about Rituxan is you can use it again and again and again with benefit on retreatment.

LIZETTE FIGUEROA RIVERA:
We'll actually take our final question today from the web audience. Billy asks, do you think indolent lymphomas will ever be curable?

DR. OWEN O'CONNOR:
So I think with time I'm, as a MD, PhD, confident that science can find solutions to all sorts of problems. And I think with time, as we count on important organizations like the LLS to fund research in the field—and I know they are actively funding research in understanding cancer stem cells and the concept, which I didn't introduce today, is other ways to sort of target those stem cells or those cells that don't die with chemotherapy, while some do.

I think in time science will find the answer and could well find strategies to cure the disease. We do know that allogeneic stem cell transplant will cure follicular lymphoma, so that we know. So we know that in the context of an allogeneic stem cell transplant, where you're introducing an immune system from your brother or next-door neighbor, that difference in the immune system's recognition of the disease can lead to cure. So there are exciting new immunotherapies that are here and emerging that may offer that prospect in time.

I think the question I would ask is, do we have to cure the disease? Because when it comes to managing indolent lymphomas, I always tell people, don't be seduced into thinking about it the way you had to think about your, you know, parents who were diagnosed with a lung cancer or a colon cancer. In those situations, if the disease metastasises, it's a challenge to manage. But in the case of these diseases, where the median ages can be in the 60s or in the case of CLL in the 70s, if we can give you a pill to manage your disease, I would say that's a victory. And if we can convert your disease to something that can be managed readily, the way you manage hypertension or diabetes—and I don't mean to belittle a diagnosis of cancer—but I think that we are moving toward a period where some of these diseases can be managed like chronic illnesses. And with the advent of oral therapy that is safe, effective—drugs like idelalisib, drugs like ibrutinib, drugs like ABT-199, and the cocktail of emerging antibody drug conjugates I think afford us a good opportunity to manage the disease safely without major impacts on your quality of life and can be managed very conveniently.

So I would say that I'm confident science will solve that problem. I think it's going to take time. But in the interim I would say, eh, I don't think it's the most important issue in the universe. I think we have a exciting variety of approaches to manage the disease and really turn it into a chronic disease, which I think is an absolute victory.

LIZETTE FIGUEROA RIVERA:
Thank you, Doctor. Thank you, Billy, for your question. And thank you all for your questions. And Dr. O'Connor, thank you for your continued dedication to lymphoma patients. You and your colleagues' research, successes, as well as patients' access to better treatment have really made a great impact on people's lives.

DR. OWEN O'CONNOR:
Thank you.

LIZETTE FIGUEROA RIVERA:
Sure, thank you for being with us today. And we hope this information will assist you and your families in your next steps.

Slide 80. LLS Resources

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

The Leukemia & Lymphoma Society also has a Copay Assistance Program for lymphoma patients. To find out if you qualify, please call 1-877-557-2672, where a Copay Specialist will assist you, or you may apply online at www.LLS.org/copay.

Dr. O'Connor, 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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