Living with Lymphoma

Guest Expert:
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Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and he is an internationally recognized expert on colorectal cancer. Dr. Foss is a Professor of Medical Oncology and Dermatology and she is an expert in the treatment of lymphomas. If you would like to join the discussion, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Dr. Chu welcomes his co-host Dr. Francine Foss for a conversation about lymphoma.

Chu: Francine, before we discuss the main topic of lymphomas, can you tell our audience a little bit about what made you decide to focus on lymphomas as your treatment specialty?

Foss: I have been interested in lymphoma pretty much from the time I started my medical training. I think it relates to the fact that I have always been interested in the blood and white blood cells for some crazy, crazy reason. When I was at the NIH I got very involved in the lymphoma program and in fact I took over the T-cell lymphoma program there, both the clinical as well as the research component.

Chu: As we have said before on the show, you and I trained together at the NCI a number of years ago and what was really special back then, and maybe a part of why you decided to focus on lymphoma, is that at the time we were there the National Cancer Institute was the leading place, the Mecca, for developing new treatments for Hodgkin's and non-Hodgkin's lymphomas.

Foss: That's right Ed, and in fact, Vincent DeVita who was our leader at the NCI at that time and has subsequently come to Yale Cancer Center, was one of the major leaders in developing the treatments that we use today for lymphoma. In addition to that, at the time that I was there the NCI did a very important pivotal study exploring whether or not chemotherapy and radiation therapy was beneficial for patients with low-grade lymphoma. This has been a landmark study to help us to know how to treat those patients even today, 20 to 25 years later.

Chu: Maybe you can tell us what lymphoma is and what the different types of lymphomas are that people should be aware of?

Foss: Lymphoma is really a generic term and it incorporates a number of different diseases. A lymphoma is a disease of white blood cells; however, unlike leukemia, which is also a disease of white blood cells, lymphoma predominantly occurs in lymph nodes or in organs like the liver or the spleen, whereas leukemia primarily occurs in the bone marrow and in the blood. Lymphoma comes in a number of different varieties. There is B-cell lymphoma,

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which is the more common type and is about 85\% of the non-Hodgkin lymphomas. Then there is the T-cell type, which is 15\%, and then there is another whole category called Hodgkin disease, which comprises about 25\% of lymphomas. All of these lymphomas have different subtypes under those general categories as well.

Chu It has gotten a lot more complicated since you and I were fellows back at the National Cancer Institute.

Foss That's right, and it’s becoming even more complicated now that we understand the genetics of some of these types of lymphomas, because what we are now doing is dissecting them even further and identifying subgroups based on different kinds of genes that are expressed, or different patterns that the cells express. We are now taking categories and making more categories and more categories, and the real value of that, particularly from the point of view of a patient, is that we are learning that the treatment for some of these categories is different.

Chu Obviously we have been aided a great deal by our understanding of the basic biology and the molecular genetics of these different lymphomas.

Foss That's right, and in fact, lymphoma is one area in cancer where we have developed a lot of novel approaches and where we were first able to understand the genetics and subgroup two different types of lymphomas in the diffuse large B-cell category that have completely different prognoses. Also lymphoma is the disease where we first learned how to use monoclonal antibodies, and in fact rituximab, which is for B-cell lymphoma, was one of the first antibodies that came into the clinic.

Chu About how many people each year are diagnosed with Hodgkin’s and non-Hodgkin’s lymphomas?

Francine The American Cancer Society estimates that there are about 53,000 cases of non-Hodgkin’s lymphoma in the United States. That basically translates into over your lifetime, you have about a 1 in 50 chance of developing these lymphomas.

Chu Wow.

Foss 95\% of those are in adults by the way, and 5\% are in children.

Chu What do we know about the causes for the lymphomas?

Foss We know a little bit more about the causes of lymphoma now then we used to. One of the

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things that we have learned is that there are certain viruses that can predispose patients to lymphoma, and those include viruses called EBV virus and also the hepatitis viruses in some cases can be causative. We also know that other environmental conditions can predispose people to lymphoma. For instance, we know that if you have an infection in your stomach called H. pylori, that can predispose you to a lymphoma of the stomach, and we also know that there are certain environmental exposures that can lead to lymphomas or other diseases, particularly chemical and pesticide exposures.

Chu It is interesting that farmers who are exposed to pesticides and herbicides, especially in the Midwest, seem to have an increased risk for developing non-Hodgkin lymphomas.

Foss That's right, and one of the interesting things that we have learned, and in fact this was discovered at the National Cancer Institute while we were there, is that if you look at those farmers in the Midwest that are exposed to a lot of herbicides and pesticides, we can actually detect abnormalities in their chromosomes before they develop lymphoma. Not all of those patients will develop a lymphoma, but clearly we can link a chemical exposure with a chromosomal abnormality in the genes and then later development of lymphoma. This is also pertinent, by the way, for Vietnamese veterans who were exposed to Agent Orange, because we know that Agent Orange exposure can lead to the development of both Hodgkin's disease as well as non-Hodgkin's lymphomas.

Chu Over the past few years there seems to have been an increasing incidence of non-Hodgkin's lymphomas. Do we know why that may be happening?

Foss There are a number of reasons for that. One of which is that the incidence of developing a lymphoma increases as you get older, and with the baby boomer generation aging and we are all living longer, there’s a greater chance to develop lymphoma; that's number one. Number two is that as we all know, there are many more toxins in our environment in terms of exposures in the air, in the water, everywhere, even in the food that we eat, and one cannot help but think that that's contributing to the increased incidence of lymphoma. Also, one could think about the increased frequency of some of these viruses in the population that might also be leading to the development of the lymphoma.

Chu Is there any genetic component to the development of lymphomas?

Foss There isn’t as clear-cut a genetic component to lymphoma as there is with other cancers, say like colon cancer for instance, but we do know that there are familial clusters of lymphoma and we also can see lymphomas in these family cancer syndromes where other members of the family could have ovarian cancer, colon cancer, or lung cancer. Certainly there is some

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genetic component to the disease, and with respect to the genetics, I would like to just mention one other thing that's really interesting. That is that the group at the National Cancer Institute and at Yale have been working together for years to look at the genetic predisposition to cancer, and particularly to lymphoma, and what we found is that there are certain types of genes or patterns of gene expression, what we call snips, that actually predict who is going to develop a non-Hodgkin's lymphoma. A lot of these genes are related to the immune system and how our body responds to various toxins.

Chu That's interesting. Are these tests easy for an individual to be tested for, these snips, as you call them?

Foss Yes, in fact this only involves saliva or a blood test. A major study was done in the State of Connecticut where they collected samples from over 2000 patients and normal controls, and that's the so-called "hair dye study" that you may remember from a number of years ago where they thought there might be an association between the use of hair dyes and non-Hodgkin's lymphoma. Subsequent to that study, hair dye preparations have been changed, so everybody can relax about that, but in the course of collecting that data, we learned a lot about the genetics of lymphoma in this population.

Chu Let's switch gears a little bit and talk about the common symptoms that an individual who is diagnosed with lymphoma may present with.

Foss Lymphoma is an interesting disease because it can present with very significant symptoms, or no symptoms at all. In fact, many of the patients that we see come into our office because they noticed a lump, or their primary care doctor, in the course of a normal exam, noticed a swollen lymph node. Some of those patients also come to us because there was an abnormality in their blood test. For instance, they may have had an elevated white blood count or they may be anemic. On the other side of the coin are the patient's who come in with aggressive lymphoma or symptomatic lymphoma, and generally speaking, those patients can have weight loss, fevers, night sweats, or they can have other symptoms that are related primarily to the growth of lymph nodes that might be putting pressure on other organs and causing those symptoms.

Chu A common complaint would be swollen, tender lymph nodes in ones neck for example. What would you tell someone who may be listening right now who has fever, sweats, and has a very tender lymph node?

Foss Well, we all have to remember that the most common cause for a swollen lymph node, a sore throat, fevers and chills, is an infection, and in fact, what most primary care doctors do is

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observe those patients and maybe treat for an infection. Then, if those symptoms don’t resolve themselves over the course of a couple of weeks or a month or so, and the lymph node is still swollen, in that case you might want to seek medical attention and be a little bit more aggressive. But there are certain conditions like mono, which we are all familiar with, where you can have swollen lymph nodes for weeks or months, and that doesn’t necessarily mean that you are going to develop a lymphoma.

Chu So the good news for our listeners out there is that in the vast majority of cases where you have got swollen lymph nodes, it is really probably nothing to worry about.

Foss Exactly.

Chu What would be the different types of diagnostic methods that you would use, or consider, in trying to make a diagnosis of lymphoma?

Foss The primary diagnosis of lymphoma is made based on examining a piece of tissue under the microscope, and that usually involves getting a lymph node biopsy. However, if the lymph nodes are all internal, what we can do is what we call a needle biopsy where we just pass a small needle in and we obtain a piece of tissue.

Chu Now, who would usually do that diagnostic procedure, that biopsy?

Foss The biopsy is either done by a surgeon or by interventional radiology. It is important to note that when you do get a biopsy, that biopsy needs to undergo a number of different steps with respect to looking at the pathology because it can be tricky sometimes to distinguish lymphoma for what we call a benign lymphoid proliferation.

Chu And I imagine that as we have a bit more understanding of the molecular genetics and there is a much deeper understanding of the molecular classification of lymphomas, clearly it is going to be important to have a pathology group that is very sophisticated in the types of diagnostic techniques that they have at hand.

Foss Exactly, and as I mentioned at the beginning of the show, we are now dissecting these lymphomas into categories based on different genes that they express. We can look at a number of these different parameters just by looking at the tissue under the microscope because we have special stains. We also can do molecular studies on this tissue to look for the expression of certain genes that will help us to categorize those lymphomas, and that directs our treatment.

Chu You are listening to Yale Cancer Center Answers. I am here in the studio with Dr. Francine Foss, my co-host, and one of the nations leading experts in the treatment of lymphomas. At this point we are going to take a break, and at the outside of the break we are going to then focus our discussion on new treatment strategies for lymphomas.

Medical Minute Breast cancer is the second most common cancer in women. About 3000 women in Connecticut will be diagnosed with breast cancer this year, but earlier detection, non-invasive treatments, and new therapies are providing more options for breast cancer patients and more women are able to live with breast cancer than ever before. Beginning at age 40, every woman should schedule an annual mammogram and you should start even sooner if you have a risk factor associated with breast cancer. Screening, early detection, and a healthy lifestyle are the most important factors in defeating breast cancer. Clinical trials are currently underway at federally designated comprehensive cancer center such as the Yale Cancer Center to make new treatments not yet approved by the Food and Drug Administration available to patients. This has been a medical minute and you will find more information at yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut Public Radio.

Chu Welcome back to Yale Cancer Center Answers. This is Dr. Ed Chu and I am joined by my co-host Dr. Francine Foss discussing the approach and treatment strategies for lymphomas. Before the break we were talking about how to make a diagnosis of lymphoma, Francine can you talk a little bit about the different types of x-rays and imaging studies that go into helping us evaluate a patient with lymphoma?

Foss Sure, and that's a very-very important point with lymphoma because the way we treat it really depends on the stage; stage meaning how far it has spread. We look at patients from the point of view of stages I through IV. We determine the stage based on x-rays of the lymph node groups at the liver and the spleen. We used to use CAT scans for that and now we have a new and more sophisticated test called the PET scan, which is actually much more sensitive at detecting very small amounts of lymphoma in lymph nodes. So we do a PET scan along with a CAT scan and we are able to look at nodes that light up using the PET tracer and we also look at the CAT scan to see if those lymph nodes are enlarged. We are also able to see the other organs with PET scan and we can see whether there is involvement of the bone or soft tissue such as the skin. All of that information goes together to come up with a clinical stage.
What is the overall prognosis for patients with lymphoma? I imagine it must be in some way correlated with the stage of the disease.

The prognosis for lymphoma is highly variable and it depends on the type of lymphoma that you have as well as the stage. For instance, patients with a low-grade B-cell lymphoma have a survival that's really the same as a normal population, so they could have this disease for 25 to 30 years, and in some cases, not even require treatment. On the other side, there are the very aggressive lymphomas which require immediate treatment and in some cases with some of the aggressive T-cell lymphomas, the survival is not good even after conventional chemotherapy type approaches.

Maybe break down what the general treatments strategies for an individual who presents with lymphoma are?

The treatment for lymphoma can involve anything from watching and waiting, in the case of low-grade lymphomas, to potentially using radiation therapy for patients that have localized lymphomas, to the use of chemotherapies, conventional chemotherapies, such as a single-agent drug like fludarabine or a combination such as CHOP. In some cases, we use more aggressive combinations such as EPOCH which require hospitalization, and in some cases we even go to a more aggressive approach which is to follow the chemotherapy with a stem-cell transplant. There are many patients with lymphoma who will receive both radiation and chemotherapy, and then after that the treatment is not over for a lot of patients because we do maintenance therapy, particularly for patients with low-grade lymphoma where we know that the use of the monoclonal antibody rituximab can prevent those patients from recurring.

It sounds like in your description that there is no role for surgery at all in the treatment of lymphomas?

That's a very good point, and it's something that a lot of patients ask about. They say, “I have this lump, why don’t we just take it out?” Well, we know that lymphoma is a systemic disease. Even if we only find it in one place, we know those cells can travel around in the blood, so taking one lymph node out isn't necessarily going to solve the problem. In fact, in patients with localized lymphoma, where we take out one node because we make a diagnosis and we find nothing else, often times we will follow that up with either involved radiation to that area of the body, or may be even something like rituximab or some chemotherapy.

Over the last few years we have talked a great deal about the development of target therapies, in particular for breast cancer, lung cancer, and colorectal cancer, my own area of expertise.

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but without question targeted therapy really has a very important role in the treatment of the lymphomas.

Foss

That's right, and as I mentioned, the CD20 antibody rituximab was really the first targeted therapy to be used in this county, and that is for patients with B-cell lymphomas. One of the things about lymphomas is that they are basically white blood cells and they do express a lot of proteins that we can generate antibodies against, but the problem is that the normal cells may also have the same antigens. So the trick is to administer a targeted therapy that's going to kill the tumor cells without killing too many of the normal cells. Now, we are lucky with rituximab, because that seems to work, but there are other antibodies that we have developed for lymphoma, such as antibodies against the CD4 protein, that eliminate not only the tumor cells, but also lots of the normal cells as well. I would like to put in a plug for T-cell lymphomas here because it really is the most underrepresented lymphoma in terms of research in the United States. If you look at the number of cases of T-cell lymphoma it is 9500, and the number of cases of Hodgkin’s disease is actually 8500. There are more cases of T-cell lymphoma than Hodgkin’s disease, but if you ask the average person on the street, they have heard of Hodgkin's disease, but many people do not hear very much about T-cell lymphomas. Unfortunately, T-cell lymphomas can be among the most deadly lymphomas.

Chu

You also have been very actively involved in, as I said, developing new treatments, and in fact you played a leading role in the approval of a number of new agents that are approved for these T-cells lymphomas.

Foss

That’s right, we developed the first fusion toxin which specifically targets a lymphocyte, and that's the ONTAK molecule that targets the CD25 receptor on T-cells. This has proven to be a very important molecule in the treatment of patients with both cutaneous T-cell lymphoma and now aggressive T-cell lymphoma. We have taken this molecule and combined it with chemotherapy for patients with aggressive PTCL and we have shown that their response rate is very high, much higher than with chemotherapy alone, and now we are trying to exploit this strategy to combine that targeted molecule with others so that we can specifically target pathways in the lymphoma cell that will lead to cell death.

Chu

Do we know, Francine, why the lymphoma develops, or focuses on the T-cell as opposed to the B-cell?

Foss

The interesting thing about T cells is that our body uses T cells for what we call immune surveillance. In other words, there are T cells living in all of our tissues and those T cells recognize foreign antigens or proteins and generate an immune response. For instance, in the mucosa, in your mouth and in your stomach, in your intestines and in your skin, there are lots

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of normal T cells and so you could think about that in terms of the chance of a cell becoming mutated. If there are lots of T cells that are always looking for foreign proteins, they are dividing quickly and if they are turned on then there is a greater chance that you are going to develop a problem or a mutation and then develop a lymphoma, and in fact, we do see T-cell lymphomas in a lot of these extra-nodal sites such as the skin, the GI tract, the liver, the mouth for instance, and so they tend to be atypical in terms of their presentation.

Chu Interesting, tell us a little bit about the role of radioactively labeled antibodies because that's becoming a very hot area.

Foss So to speak.

Chu Right.

Foss Radioactive antibodies have been used in the treatment of B-cell lymphoma, and again, we’ve used the CD20, which is the antigen that the rituximab molecule targets. We have basically taken that rituximab antibody and hooked it up to radioactivity in the form or either an yttrium or an iodine isotope, and the reason we have done that is that the antibody can act as a carrier to deliver the radioactivity specifically to the sites of tumor, and then that radioactivity can be very powerful in terms of killing those cells say in lymph nodes and in other sites of lymphoma.

Chu Does that radioactive label ever get clipped off and cause problems with normal tissues?

Foss It’s interesting because you and I were both at the National Cancer Institute when we first started to develop these radioactive antibodies, and in fact, one of the problems we had in the first clinical trials is that there was a dissociation between the radioactivity and the antibody, but the technology has improved significantly since that time such that now that does not appear to be a problem at all. We do not detect any free isotope that's not hooked up to the antibody.

Chu Is there ever any concern that if a patient is treated with radioactive antibody, that their family members or their friends, or relatives may be exposed?

Foss This is obviously a big concern and the Nuclear Regulatory Commission is involved in our use of these antibodies in the clinic, and what we know is that the exposure to radioactivity to other people is very minimal. The major risk that we run is really in the first 24 to 48 hours and we generally tell patients not to go home on a bus and don’t have a child sit on your lap, maybe you want to stay in your room for 24 hours, but pretty much after that you are safe to

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be exposed to people.

Chu Francine, tell us a little bit, as we are kind of a heading towards the end of this interview, about the clinical research that you are focused on at Yale Cancer Center.

Foss We have a significant number of trials now available for patients with both B-cell and T-cell lymphomas, and we are focusing on developing novel therapies for patients. For instance, we have a trial looking at the use of histone deacetylase inhibitors, which is a novel molecule in patients with both B and T-cell lymphoma. We are also developing a strategy to use small molecule inhibitors of tyrosine kinase in lymphoma. We are now opening a study using a molecule called sorafenib. In addition to that, we are looking at the use of transplantation and we are developing novel strategies to do transplant in patients with both B and T-cell lymphoma. Our major focus is really on trying to develop novel therapies, but also learning how to use some of the drugs that are currently available in different ways.

Chu Maybe a quick word about the transplant work that you were doing when you originally were at Tufts-New England Medical Center, and then coming here to Yale you helped to develop a very novel approach to try to prevent graft-versus-host disease, which is still a very significant problem in stem cell transplantation.

Foss That's right, and in fact, if you look at the overall outcome after transplantation, particularly for lymphoma patients, the major cause of death is really the complications of transplant. So we are looking at using a treatment called photophoresis with the conventional transplant regimen and our outcomes using that approach have been excellent.

Chu Francine, the time has gone pretty quickly and we are at the end of the show. Obviously we look forward to having you come back and talk more about new treatments for lymphoma.

Foss Thank you Ed, it's been a pleasure to talk with you tonight.

Chu You have been listening to Yale Cancer Center Answers and I would like to thank my co-host and tonight's guest expert Dr. Francine Foss for sharing her expertise on the treatment of lymphomas. Until next week, I am Ed Chu from Yale Cancer Center wishing you a safe and healthy week.

*If you have questions or would like to share your comments, go to yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.*