

Yale CANCER
CENTER
answers

WNPR Connecticut Public Radio



Hosts

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**What to Expect when
Diagnosed with
Lymphoma**

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Yale Cancer Center Answers

is a weekly broadcast on

WNPR Connecticut Public Radio

Sunday Evenings at 6:00 PM

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Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Ed welcomes his co-host Dr. Francine Foss. Dr. Foss is a Professor of Medical Oncology and Dermatology at Yale Cancer Center and this evening she'll be discussing her specialty, lymphoma. Here is Ed Chu.

Chu Francine let's start off by having you describe for listeners out there, what made you decide to specialize in hematologic malignancies, which are also known as liquid tumors?

Foss It really dates back to my interest in looking at blood under the microscope, which started at a very early age, but then when I went to the National Cancer Institute I was very impressed by Dr. Vincent DeVita, who formally was the Cancer Center Director here at Yale Cancer Center. Vince was the Director at the National Cancer Institute and a world leader in developing therapies for lymphoma. We had a very strong program in lymphoma at the NCI and I got interested in doing some basic research in lymphoma and from that I went on to develop a specific interest in the T cell lymphomas.

Chu I think many of our listeners may know that Dr. Foss and I actually trained together at the National Cancer Institute in the 1980s and as you say Francine, the National Cancer Institute at that time was the Mecca for lymphoma research, and so I can see how that generated a great deal of enthusiasm on your part.

Foss Exactly, and it was a tremendous pleasure to be able to work with somebody like Dr. DeVita.

Chu It was amazing, obviously Dr. DeVita as Director of the NCI and leading the lymphoma research effort, but it was really a whose who of the lymphoma experts in medical oncology, radiation oncology, who were there in Bethesda at that time.

Foss Exactly, and another area that was specifically strong was the pathology and in fact, Dr. Allan Jaffe has been one of the key people in developing the new lymphoma classification system, and I think that's one way that lymphoma has really changed over the last 15 or 20 years. We started out with a very basic classification system of low, intermediate, high grade, B cell lymphomas, and T cell lymphomas and now we have got the WHO classification system that has broken these diseases down into very specific

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entities based on new information about the molecular characteristics of these different tumors.

Chu It seems to me what has really evolved to the greatest extent is our molecular understanding of the molecular genetics and the biology of these various lymphomas.

Foss Exactly, as we have done more and more genetic testing and learned more about the biology of these different subtypes of lymphoma, we now have many, many different categories and many specific names for these different subtypes.

Chu Obviously it's a very complicated field, but for our listeners can you break it down very simply as to the different types of lymphomas that you deal with?

Foss Basically you can think about lymphoma in broad categories, first of all Hodgkin's and non Hodgkin', then when you go beyond that and look at the non Hodgkin's lymphomas, which are by far the more common types, they basically breakdown into the B cell and T cell types and within each of those categories there are lymphomas that are low grade or have a low grade behavior in the patient, an intermediate grade, and then the high grade lymphomas and then within each of those categories there are number of different subtypes as well.

Chu How common is lymphoma as a disease?

Foss It's surprising, and most people don't think about this, but lymphoma is the fifth most common malignancy in the United States. Within the state of Connecticut, there is an average of a thousand cases per year and that number is increasing not only here in Connecticut, but overall in the country as well.

Chu Why is the incidence of lymphoma increasing here in the state of Connecticut?

Foss The incidence is increasing overall for a couple of different reasons, one of which is that we are living to be older, and if you look at both lymphoma and other hemological malignancies like leukemias, the incidence increases as you get older. Part of the reason for that is just accumulation of different events, toxic exposures and events that happened to these cells that are dividing all the time. With respect to specific risks for lymphoma, we have identified a number of things, first of all various chemical and toxic exposures in the environment, and we all know that there are obviously

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more of those with processed foods and chemicals going into the air and water, so that's a definitely a risk factor. There are also specific risk factors with respect to infections, particularly viral infections, that have been associated with lymphoma and this is something that people don't normally think about.

Chu On that point Francine, what are some of the viruses that have been shown to increase the risk for developing lymphoma?

Foss We know specifically that EBV viruses are associated with the development of B cell lymphomas and we have also identified recently that hepatitis C can be a risk factor for the development of lymphoma. We also know about HTLV-1, which is a virus specifically associated in the Caribbean and Japan but also in certain populations in the United States and that is associated with T cell Lymphoma, and other risk factors are things like environmental exposures and things like H. pylori, which actually is bacteria that can colonize the stomach. We know that H. pylori is associated with the incidence of gastric lymphomas.

Chu EBV is Epstein-Barr virus and it is typically associated with the development of infectious mononucleosis, is there any association between the development of mono, which is obviously pretty common in the general population and subsequent development of lymphoma of any kind?

Foss No, there really is not a specific association, but we know that all of us are exposed to the EBV virus at some point in our childhood. We can actually find that virus in our cells but it remains dormant in most people. In some circumstances, related to perhaps some defects in the immune system, the virus can become activated and that leads me to the discussion of the association of lymphomas with patients who are immunocompromised, so certainly patients with HIV have a higher incidence of lymphoma because they don't have an intact immune system. Also now that we are using a lot of immunosuppressive drugs in various situations, such as patients who had organ transplants, kidney, or liver, or heart transplant they are on these medications for a long time and they have an increased incidence of lymphoma. Also now we are starting to use these immunosuppressive medications in other diseases such as psoriasis and rheumatoid arthritis and we are now starting to see an increased incidence of lymphoma in some of those populations as well.

Chu In that setting, when we are using immunosuppressive agents, is it the

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duration or the extent of use that really increases the risk for developing lymphoma?

Foss It perhaps is related to the duration, but there are other host factors as well such as your genetic susceptibility to develop lymphoma.

Chu What do we know about the genetics of lymphomas? If a particular family member was diagnosed with non Hodgkin's lymphoma, is there then an increased risk for other family members to develop lymphoma?

Foss We really don't know as much about genetic risks with lymphoma as we do about other diseases such as breast cancer, for instance, where we identified the BRCA1 and BRCA2 genes and we can predict with certainty that there is going to be an increased risk in other family members. With lymphoma we do see family clustering cases, but we really do not have specific genetic information that we can use to screen and follow patients.

Chu Granted there are many different types of lymphoma, but are there any general symptoms that patients may present with at the very beginning of the disease?

Foss One of the problems with lymphoma is often times the patient is asymptomatic, and patients will come to medical attention either because they have identified a lump or lymph node or they have gone in for a blood test for some other reason and something has been identified. In the case where a patient is actually symptomatic with lymphoma we identify what we call B symptoms and B symptoms specifically would be things like fevers, weight loss, fatigue or night sweats. So if those things occur, those certainly would raise our index of suspicion to look for a lymphoma.

Chu And on a physical exam what are some of the abnormal findings that might develop?

Foss Well, one of the other things about lymphoma that is confusing for patients is that not all lymphomas actually occur in lymph nodes. Certainly if there are enlarged lymph nodes one might feel those say in the neck or under the arms or perhaps in the groin, but first of all many of our lymph nodes are internal and they are not even palpable, and so the only way that we might know that they are enlarged is if they are putting pressure on other tissues or other organs, but generally speaking that does not happen unless the lymph nodes are really large. As I mentioned lymphomas can occur in areas other than lymph nodes as well and it might occur simply as an enlargement of the

spleen which might be symptomatic because the patient may feel full after eating and the spleen is pressing up on the stomach or an enlargement of the liver, and in some cases lymphoma can also present just in the bone as bone pain or even in the skin as a skin rash or skin nodules.

Chu Francine, I know a lot of us will periodically have lymph nodes in the neck region usually associated with a sore throat or upper respiratory infection. When does one have to begin to worry that this is more than just a simple infection?

Foss Generally speaking I would say persistence of that lymph node over the course of weeks, certainly if it has been a month and that lymph node has not resolved, one should definitely seek medical attention.

Chu If there is a lymph node that results because of lymphoma, is that lymph node generally tender or nontender?

Chu I just want to make one point about that, there is a type of lymphoma called low grade B cell lymphoma where lymph nodes can actually be waxing and waning in the patient without medical personnel doing anything, so you may notice the lymph node and then it may go away by itself and then it may come back, so that kind of pattern of waxing and waning is something that we do watch out for. Generally speaking, if it is due to say an infection a lymph node should resolve over the course of 3-4 weeks. It may or may not be tender so even in the setting of having an infection you may have a lymph node that's not tender, but certainly if it is tender that would make us think more about infection and less about lymphoma.

Chu And then obviously if the suspicion is high that an individual may have lymphoma what's the typical evaluation process that needs to be done?

Foss The first thing that needs to be done with any patient is obviously to see a physician and get a biopsy. We effectively can not make the diagnosis of cancer without seeing it under the microscope, so we either need a piece of tissue such as a lymph node or in some cases there may be specific findings in the blood that would lead us to the diagnosis such as the presence of some circulating cells that are lymphoma cells that we can detect in the blood, but I would say by and large most patients are diagnosed based on getting the lymph node biopsy. This can be done either by a needle or a core of the biopsy, or preferably by a biopsy itself. Sometimes these needles can be suggestive but not diagnostic of lymphoma and we actually do need to go and get a piece of the lymph node.

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- Chu This would be a surgeon generally who does this biopsy?
- Foss The needle biopsies may be done by a radiologist, but effectively we end up with the surgeon in the end because we do need to get a piece of tissue.
- Chu If the surgeon does the biopsies, the pathologist reviews it and says this is consistent with lymphoma of some kind, what other evaluations need to be done?
- Foss The pathologist is a very important person in this whole evaluation because the whole diagnosis depends on a number of factors that we get from the pathologist. It's not enough just to see atypical cells any more. We really are looking for specific genetic markers as well. The first step is to get effective pathology and review that pathology if there are questions about the diagnosis. The first point I would like to make is to make the diagnosis of lymphoma and to make sure that this is not a benign condition that has been confused with lymphoma.
- Chu We are going to take a short break now for a medical minute. Please stay tuned to learn more information about the evaluation and treatment of lymphoma with my guest and co-host Dr. Francine Foss.

*Medical
Minute*

There are over 11 million cancer survivors in the US and the numbers keep growing. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life changing experience. Following treatment return to normal activities and relationships may be difficult and cancer survivors may face other longterm side effects of cancer including heart problems, osteoporosis, fertility issues, and increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers such as Yale Cancer Center to keep cancer survivors well and focused on healthy living. This has been a Medical Minute brought to you as a public service by Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

- Chu Welcome back to Yale Cancer Center Answers. This is Dr. Ed Chu and I am here in the studio with my co-host and guest expert Dr. Francine Foss who joins me to discuss the topic of lymphoma. Before the break, Francine, we were talking about the biopsy procedure being done by the surgeon and the critical role of the pathologist. For those who missed it, can you re-

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discuss the role of the pathologist and how to make the diagnosis of lymphoma?

Foss The pathologist will be evaluating the tissue and they will be looking at specific markers on the tumor cells or on the cells in the tissue to try to identify if those cells are tumor cells. Now one of the confusions with lymphoma is that these are basically tumors of lymphocytes and in some cases these lymphocytes don't look different under the microscope, so we really need to identify specific genetic markers that can help us to make the diagnosis. The thing that we look for in both T cell and B cell lymphomas is what we call clonality, which is a rearrangement of a specific receptor, the T cell receptor or the immunoglobulin heavy gene receptor, which identifies the fact that all of those cells are essentially derived from the same cell, i.e. that is a tumor as opposed to a normal population of lymphocytes, so that's the first thing we look for. Then we look for other specific genes that can identify the specific subtype of lymphoma and we do have some types of lymphoma such as mantle cell lymphomas where there is a specific gene called Cyclin D1 that help us to identify that specific lymphoma, and we also have T cell lymphomas such as the ALK-positive anaplastic large-cell lymphoma where there is a similar marker. I would like to say also for the audience that we do actually biopsy a number of lymph nodes that are called pseudolymphoma that are not actually lymphoma and we believe that these are a benign proliferation of cells that don't actually go on to lead to lymphoma, so not all of the patients that are referred to me as a lymphoma doctor actually have lymphoma.

Chu In 2010 the current standard of care as part of the evaluation process is for all of these genetic tests to be done on that biopsy specimen.

Foss Exactly there are many, many tests that are done in addition to looking under the microscope.

Chu So once all of those tests are done and you have a diagnosis, the definitive hard diagnosis of lymphoma, what's the next step?

Foss The next important thing to do is what we call staging, and that is to see how extensive the disease is and we do that by obtaining either CAT scans or PET scans and oftentimes also by getting a bone marrow biopsy to see if any of the cells are in the bone marrow.

Chu What are the different treatment options that are available to you now as a

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medical oncologist?

Foss There are many, many treatment options for lymphoma and they run the gamut from doing nothing, which is watching and waiting which we do in patients with low grade B cell lymphoma, to doing radiation of a single lymph node area to doing chemotherapy or possibly even aggressive chemotherapy and a bone marrow transplant. It really depends on what kind of lymphoma you have and how extensive that lymphoma has spread at the time of diagnosis.

Chu Some of our listeners out there may be scratching their heads and saying, you have someone with lymphoma, you say low grade lymphoma and one of the options may be to do nothing?

Foss This has really been paradigmatic for a lot of us as physicians as well, because when you and I were back at the National Cancer Institute, a very large and pivotal clinical trial was done for patients with low-grade B cell lymphoma, and those patients were randomized to either receive a very aggressive chemotherapy regimen along with radiation to all of their lymph nodes in an attempt to cure them. In the other arm of the study, patient's got no treatment and they were followed for their disease and if they did develop symptoms they may have had some very mild chemotherapy or very limited radiation. Everybody at the time we initiated that study thought that the patients on the aggressive arm would do better and live longer, and what ended up happening at the end of the day is that there was absolutely no difference in survival, and so that has really changed our thinking about low grade lymphoma and in fact, the way we approach low grade lymphoma now is to either watch and wait the patient if they have no symptoms or if they do have symptoms to treat them with biological therapies rather than chemotherapy. I am referring specifically to the monoclonal antibody rituximab which targets CD 20 on the surface of those cells.

Chu And that antibody therapy really has revolutionized the treatment of lymphoma.

Foss The major step forward that we made in the last 20 years with lymphoma has been the implementation of that monoclonal antibody rituximab, not only by itself for patients with low grade lymphoma, but also in combination with chemotherapy as a first line therapy for patients with diffuse large B cell lymphoma where we have were shown that we can cure a significantly larger number of patients by combining the antibody with the chemotherapy, and then the third thing that has really changed our treatment is that we have

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been able to actually link that antibody to various radioisotopes to create radioimmunotherapy, which has also been very effective as a treatment for patients.

Chu This biologic therapy Rituxan, does it have any side effects?

Foss The nice thing about rituximab is that there are very few side effects other than the first dose where patients might get chills or fever or a reaction to the infusion of the medication, but generally speaking after that patients can get this medication for months or even years without having any significant side effects from it.

Chu It's really very different than the traditional chemotherapy like the standard cancer agents that you and I have been so accustomed to for the last 20-25 years?

Foss Exactly, and what's really important when you think about this as a patient is you really need to know what the goals of therapy are for your specific type of lymphoma, so for instance, if you have diffuse large B cell lymphoma which is an aggressive disease, you would not be treated just with this antibody therapy; you would need chemotherapy. And if you have low-grade lymphoma and it's the type of low-grade lymphoma that can be followed or treated conservatively, then you do not need chemotherapy.

Chu What's really remarkable about the treatment of lymphoma when you look at just say the last 5-10 years is there have been dramatic advances in the number of new treatments, new drug regimens, and new agents that have been approved to treat lymphoma.

Foss That's very true and I think this is a very exciting time to actually be in the field of lymphoma. Rituximab, we mentioned, was a huge step forward, but if you look over the last 3-4 years, particularly over the last year, there have actually been 3 or 4 drugs approved for lymphoma. One of the drugs that was approved is bendamustine and that was actually approved a couple of years ago and the thing about bendamustine is that recently it was used with rituximab and compared to rituximab plus CHOP, which is aggressive chemotherapy, it showed that the results were the same, and the nice thing about bendamustine is it does not have the side effects such as hair loss and other side effects associated with chemo, so that was a huge step forward. We also had another monoclonal antibody called ofatumumab approved. This was actually approved for CLL, chronic lymphocytic leukemia, but it also targets the CD 20 that rituximab targets so I think we are going to

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see that used also in lymphoma. We have also had two drugs approved for T cell lymphoma and these in fact are really important drugs because we don't have good therapies for T cell lymphoma. One of these drugs is pralatrexate and the other drug is romidepsin, which is a histone deacetylase inhibitor, another novel biological strategy for treating lymphomas.

Chu Francine, obviously you are a world expert in the treatment of all lymphomas, but I know that you have had a particular interest over the years in the treatment and evaluation of patients with T cell lymphomas and there also have been pretty significant advances in addition to the two drugs that you just mentioned.

Foss The T cell lymphomas have generally been the forgotten lymphomas because T cell lymphoma is about 10 to 15 percent of all lymphomas, and the number of cases is about 8-9 thousand per year in the United States. There really has not been as much research on T cell lymphoma because we haven't really understood the biology, so only recently, over the last 3 or 4 years, have we been able to do molecular profiling of these tumors and identify specific subtypes of T cell lymphoma and we have also now started to tailor our treatments for these specific subtypes.

Chu We have talked about chemotherapy and biologic targeted therapy. When would you consider the role of bone marrow transplantation or stem cell transplantation in treating a patient with lymphoma?

Foss Stem cell transplantation is a very important treatment for lymphoma, and in fact, if you look at the indications for stem cell transplant in the United States, leukemia is obviously number one, but non Hodgkin's lymphoma is the second largest and the number of transplants done for non Hodgkin's lymphoma is increasing. There are basically two different types of transplant; the autologous transplant and the allogeneic. And the autologous is when you give yourself back your own cells and that's being used now for patients with diffuse large B cell lymphoma who have relapsed disease. It's also being used for patients with aggressive T cell lymphomas whereas the allogeneic transplants, or getting cells from somebody else, is used primarily for lymphoma patients who have either a very aggressive histology, or for those patients who have already failed an autologous stem cell transplant, and fortunately for us, because of advances in transplantation we are now able to transplant patients even in their 70s.

Chu One question that always comes up with the autologous transplant when you are giving back the patient's own bone marrow is whether or not there is the

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possibility that there may be contamination with lymphoma. Is there anything that's done to try to screen for that and to make sure that there are no lymphomas cells that are being infused back into the patient?

Foss This is an important question Ed, and in fact, the primary risk with the autologous transplant is relapse, so early on there was some relatively primitive strategies to try to so called 'purge' those stem cells of the tumor cells, but now that we have agents like rituximab and the radiolabeled antibodies such as Zevalin and Bexxar what we can do is administer these therapies directly to the patient and thereby purge the patient of tumor cells before we harvest the stem cells, and this is proving to be a very effective strategy for patients with B cell lymphoma. Unfortunately we do not have really great ways of doing that yet in patients with T cell lymphoma.

Chu With respect to allogeneic transplantation, what are the main side effects and complications from that procedure?

Foss That really depends on the type of allogeneic transplant. We used to do what we called ablative transplants where we gave very high doses of radiation and chemotherapy and there was lots of toxicity just associated with the conditioning regiment, and now we know that we can actually do what we called reduced intensity, or mini transplants, where we give very little chemotherapy and virtually no radiation therapy, thereby not exposing our patients to a lot of toxicity. Now the major complication of allogeneic transplant is graft-versus-host disease, which is when the new cells basically reject the body and that can cause diarrhea, liver problems, and skin rash; that's a major toxicity. We always worry obviously about the infectious complication as well. Generally speaking though we have got very good supportive care and new approaches for graft-versus-host disease and so the frequency of these complications is decreasing.

Chu You really have been one of the leaders and the pioneers in trying to develop new agents, new treatment strategies, for lymphoma, maybe you can tell our listeners out there what some of the interesting clinical trials and clinical research that your group at Yale Cancer Center are currently conducting?

Foss One of the things that we recently completed, which I think is really a important clinical trial, is the combination of a targeted T cell agent such as ONTAK with chemotherapy for patients with aggressive T cell lymphoma, and by combining these strategies we have been able to increase the complete response rate to about 90%, and that is compared to 50% without

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the targeted agent. I think that's an important strategy, and the other thing we are working on is an ongoing clinical trial now to explore the role of the histone deacetylase inhibitors combined with various chemotherapy agents and also the use of novel monoclonal antibodies and other novel targeting strategies. We are also looking at signal transduction pathways and we have a clinical trial with Sorafenib, which is a small molecule inhibitor of one of these pathways and I think that's going to be an important advance as well.

Chu If anyone listening out there is interested in hearing more or learning more information about what's going on with your hematology malignancies group, how can they get information?

Foss The information is available on the Yale Cancer Center website where we have a list of all the clinical trials that are available.

Chu Great, well Francine the time has gone fast, as always it was great having you as a guest on the show and I look forward to next week when you resume your role as co-host of the show. Until next week, this is Dr. Ed Chu from Yale Cancer Center wishing you a safe and healthy week.

If you have questions or would like to share your comments, visit 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 on the Connecticut Public Broadcasting Network.