Yale CANCER CENTER answers

WNPR Connecticut Public Radio

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Learning How to Cope with Lymphoma

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Welcome to Yale Cancer Center Answers with Dr. Francine Foss and Dr. Lynn Wilson, I am Bruce Barber. Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous 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 Dr. Wilson will interview his co-host, Dr. Foss about her work in the study and treatment of lymphoma. Here is Lynn Wilson.

Wilson Let's get started by having you tell the audience a little bit about lymphoma and what it is?

Foss Lymphoma is actually a malignancy, or tumor, primarily of white blood cells, and there are two different types of tumors of white blood cells, one of them is leukemia where the primary problem is in the bone marrow and the cell circulates it around in the blood and the other one is lymphoma where the problem is primarily in white blood cells or lymphocytes that live in lymph nodes and in other lymphoid tissues in our body. If you think about lymph nodes, we all know that we have lymph nodes in our neck and under our arms, in our groin, but we also have lymph nodes in many other areas of our body as well, including inside our body where we can even see them and also the spleen is considered to be a lymphoid organ. So, lymphomas can involve any lymphoid tissue and in fact, they can also involve nonlymphoid tissue such as the lungs, the liver, the skin, or other part of the body as well.

Wilson Does it usually start in a lymphoid tissue or can it start in another location?

Foss That's a very good question, Lynn, and often times we do not actually know where some of these lymphomas start, but very frequently we do find them in lymphoid tissues. There are some kinds of lymphomas like lymphoma of the skin for instance, that we find only in the skin, and we actually never find them in any other lymph nodes or any lymphoid organ other than the skin. I would say that they probably can arise in lymphoid areas as well as non-lymphoid tissues in the body.

Wilson How common of a problem is lymphoma in the United States?

Foss It is interesting because lymphoma is now the fifth most common cancer in the United States in both men and women and the incidence of lymphoma is rising every year and part of the reason for that is that we are all living to be older, and as the population ages, the greater the chances are that you are going to develop lymphoma.

Wilson Obviously there are a lot of different types of tumors and cancers, how did you make your career decision to specialize in cancers of the blood and lymphoma?

2:50 into mp3 file http://yalecancercenter.org/podcast/dec0510-cancer-answers-foss.mp3

Foss A lot of my career decision to be interested in lymphoma was related to the fact that I trained at the National Cancer Institute and I trained with Dr. Vincent DeVita who is kind of the father of how we treat lymphoma in the United States today. Dr. DeVita made some major advances in the treatment of lymphomas that we still use in the clinic today and also there was a tremendous amount of research in lymphoma while I was at the National Cancer Institute.

Wilson We know that there are some diseases such as lung cancer, where smoking is clearly related as a cause, are there any causative or etiologic factor associated with lymphomas?

Foss That's an interesting question, and I think it is an area that is still undergoing evolution. We know historically that certain viruses are associated with lymphoma and in fact, the HTLV-1 virus was identified from a patient with T cell lymphoma. In addition, we know that other viruses such as EBV virus, which is the mono virus, can be associated with the development of lymphomas and we also know that there is an increased incidence of lymphoma in patients that have hepatitis. But the other major cause is immunosuppression, and this is primarily in the setting of patients that have had organ transplant such as a kidney transplant or liver transplant. Many of those patients need to be on immunosuppressive medications and those medications can lead to the development of lymphoma, and likewise, in patients who have various kinds of autoimmune diseases and require immunosuppressive medications, there is an increased incidence of lymphoma as well.

Wilson Is that because under normal conditions our own body and immune system is doing surveillance and keeping ourselves in check and under control, but if we depress the immune systems, some of the lymphoid cells will start to grow out of control and cannot be kept in line?

Foss That is exactly right Lynn, in fact, the body is constantly undergoing this process called immune surveillance. There are constantly cells that are undergoing mutations in our body and our normal immune system, namely our T cell immune system, is identifying those cells as cells with mutations and is eradicating or killing those cells before they can divide and lead to a cancer. So if you suppress these normal lymphocytes, primarily these normal T cells by immunosuppressive medications, or other infections, or other kinds of insults to the system, that immune surveillance process does not go on and eventually what happens is that there are cells that can mutate and then those mutations can go on to develop into tumors, lymphomas, and in some cases solid tumors as well.

Wilson How would someone start to be concerned that they might have lymphoma? What are some of the symptoms that can go along with this disease?

Foss One of the major issues with lymphoma, unlike other cancers, is that many of our patients are actually asymptomatic. There are two types of lymphoma, there is the low grade or indolent

lymphoma and there is the aggressive lymphoma, and within each of those groups there are both T cell and B cell lymphomas, so we start dividing it into a number of different groups, but generally speaking, if you think about it in terms of low grade lymphoma and intermediate or high-grade lymphoma, most of the patients with low-grade lymphoma do not have symptoms. Many of those patients will go to a doctor for another reason and the doctor will feel that they have lymph nodes enlarged, or perhaps there is something wrong with their blood counts. On a rare instance, the patient may have a physical exam and the doctor may feel that the spleen is enlarged. In other cases, patients with lymphoma may actually find a lymph node themselves, they may find a bump that has just come up. They may also notice that they have fatigue and what we call B symptoms. B symptoms would be feeling tired, having night sweats, losing weight, losing your appetite, things that basically make you feel not well. If these things occur for more than a week or two and there is no other illness going on, then the patient should start to worry a little bit about what is going on. Now not all those patients would turn out to have lymphoma and not all patients with lymphoma have B symptoms, so that is just one indicator that the patient may have this disease.

Wilson And these lymph nodes, when they are enlarged, are they painful?

Foss Many of these are actually not painful and in fact that's one of the myths that patients have, that if they have lymph nodes that swell up, this must be cancer, in fact, not only for lymphoma, but for other cancer as well, most lymph nodes that are tender are not actually related to cancer. Many of those are related to infection. That is not to say it can't be cancer but generally speaking most lymph nodes associated with lymphoma are painless.

Wilson I know it is a complicated discussion, but tell our listeners a bit about different treatment for lymphoma and the treatments for the different types of lymphomas.

Foss The treatment of lymphoma really depends on the type of lymphoma, and that's an important point because what we really need to do to make a good treatment decision is we need to identify the specific subtype of lymphoma and we also need to identify, using various staging tests, how extensive the disease is. The first thing is to have a pathologist who can make the right diagnosis and since we now have low-grade and intermediate-grade lymphomas, we have T cell and B cell, we have gone further than that and we have a number of different entities or specific types of lymphoma within each of those categories and the treatment of each one of those is slightly different. So the first step would be to get the right diagnosis and the right subtype of lymphoma, and then the second step would be to undergo a staging evaluation and staging basically means identifying where the tumor has spread and in the case of lymphoma, we would like to get CAT scans or in some cases we could get a PET scan to look at the lymph nodes, the liver, the spleen as well as the other organs and we would determine whether the lymphoma is localized or advanced. Another thing that we would often times do, because lymphoma tends to go to bone marrow, is get

9:07 into mp3 file http://yalecancercenter.org/podcast/dec0510-cancer-answers-foss.mp3

a bone marrow biopsy, and in some cases of lymphoma we also look in the peripheral blood, we look for the presence of circulating lymphoma cells and we also look for what we call clonal rearrangements, which would indicate that perhaps there are cells in the blood. We do a very careful assessment of the patient looking at all the different places where lymphoma may have spread to and then we come up with a stage and then we actually look at the stage as well as the different subtype of lymphoma. If you want to think about it in general terms we think about the low-grade lymphomas and the higher-grade lymphomas and in a low-grade group, many of those patients actually do not need to be treated. That is something that is difficult for patients to understand, to come in and get a diagnosis of lymphoma and be told it has spread to a couple different areas of your body, but you do not actually need to be treated for this, and the idea to not treat patients with low-grade lymphoma really arises from a study that we did at the National Cancer Institute many years ago where we took patients with low-grade lymphoma of all stages and we randomized those patients either to what we call watch and wait where they did not get any treatment right away, compared to aggressive chemotherapy and radiation therapy to the various lymph nodes that were involved. As you might expect, the patients who got the aggressive treatment had a higher response rate in terms of the lymph node shrinking, but when we look at the overall survival there was no difference between the two different groups and so that lead us to believe that we could actually take these low-grade lymphoma patients and watch them without giving them aggressive chemotherapy. I will say that things have changed a lot in the last 15 years or so since we did that study, because now we have some other biological therapies for lymphoma and perhaps we'd think about treating some of those low-grade patients with these biological therapies.

Wilson It sounds like in your work, you need to be very cautious and judicious in these decisions because sometimes the treatment could be worse than the disease itself.

Foss Exactly, and often times what happens with a lot of these aggressive chemotherapy regimens that we use for patients is that they can cause mutations in cells and patients can then go on to develop other problems like leukemia, so we know that in patients who have Hodgkins disease who have been treated with a combination of radiation and chemotherapy, there is an increased chance of developing not only leukemia but also other kinds of solid tumors as well, and so when we think about the approach for lymphoma, we need to think first about what is the type of lymphoma that we are dealing with and are we going to cure that patient, and then if we are not going to cure that patient with our treatment, then we need to think seriously about the treatment that we're giving and we need to try to minimize the long term effects of those kinds of therapies on patients who are going to have the disease for 20 years or 30 years.

Wilson If I had a lymph node in my neck and my doctor was worried about it and was concerned about

12:12 into mp3 file http://yalecancercenter.org/podcast/dec0510-cancer-answers-foss.mp3

lymphoma, tell me about the procedure that a patient might go through to make that diagnosis. Would I have to be admitted to the hospital and get an operation or can it be done in the doctor's office? Do they take cells out of the node, do they remove the lymph node? What does the patient go through when this diagnosis is made?

Foss The absolute best way to make a diagnosis of lymphoma is to actually take out the lymph node so that the pathologist can look at the entire lymph node and examine the architecture of all the different types of cells in the lymph and have adequate tissue to do all the different special stains and genetic studies that we are now doing for these patients. However, we do not often times have that optimal situation. For instance, if you have a node in your neck, it is pretty easy to just get that lymph node taken out and that can be done as a surgery procedure in a day. However, if the only node that we find is deep in your abdomen, hidden behind your liver for instance, it is going to be really hard to subject a patient to a big operation to get that lymph node out, and so sometimes we will do what we call a needle biopsy and there are two different types of needle biopsies. One of them is a skinny-needle biopsy where we just get cells, and the other one is called the core needle biopsy where we actually take a little core of the lymph node and sometimes that kind of procedure is adequate to tell us if it is an aggressive or low-grade lymphoma, if it is T cell or B cell and often times that will give us the information that we need to proceed with the definitive therapeutic plan.

Wilson You had mentioned a little about markers in the pathology laboratory, how does that influence what sort of treatment you might recommend? Once you have decided T or B cell, what further pieces of information do you get when you look below the surface that might guide your recommendations?

Foss These markers are tremendously important and over the last couple of years they have become even more important. We have been able to identify specific surface markers on cells and specific genes that are mutated, for instance, or translocated genes that we can detect in these tumor cells that help to subcategorize those cells and tell us exactly what kind of tumor we are dealing with and often times that gives us important prognostic information, so for instance, a patient that has a specific type of marker on the cell may do worse than another patient with the same disease who does not have that marker, and that is important information when we decide about what kinds of treatments in terms of chemotherapy, radiation, and also even in terms of thinking about a stem cell transplant perhaps for that patient.

Wilson We are going to take a short break for a medical minute. Please stay tuned to learn more information about lymphoma with Dr. Francine Foss.

14:50 into mp3 file http://valecancercenter.org/podcast/dec0510-cancer-answers-foss.mp3

Medical Minute *Breast cancer is the most common cancer in women. In Connecticut alone approximately 3000 women will be diagnosed with breast cancer in this year and nearly 200,000 nationwide, but there is new hope for these women. Earlier detection, noninvasive treatments and novel therapies provide more options for patients to fight breast cancer. In 2010, more women are learning to live with this disease than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with the disease. With screening, early detection and a healthy lifestyle, breast cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center to make innovative new treatments available to patients. A potential breakthrough in treating chemotherapy resistant breast cancer is now being studied at Yale combining BSI-101, a PARP inhibitor with the chemotherapy drug irinotecan. This has been a medical minute, brought to you as a public service by the Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.*

Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by my co-host and guest Dr. Francine Foss. Today we are discussing lymphoma. Francine, tell us a little bit about the treatment options that are available for non-Hodgkin's lymphoma versus Hodgkin's lymphoma and how has that evolved over the last 20 years to 25 years?

Foss Most of our patients with lymphoma who are not low grade patients, but more aggressive patients that need chemotherapy, most of those patients end up getting what we call multi-agent chemotherapy, so that means they get three or four chemotherapy drugs at the same time, and often times this treatment goes on for about six cycles, or about six months of therapy. In the case of Hodgkin's disease, we use a regimen called ABVD, which has been shown to be very effective and in fact cures a significant number of patients with early stage Hodgkin's disease. In the case of diffuse large B cell lymphoma, we use a regimen called CHOP and recently we have added an antibody called rituximab to that regimen. The rituximab antibody is specifically directed against a particular protein on the surface of B-cells, namely CD 20, and this is a monoclonal antibody that will target those cells specifically. Now the rituximab, as I mentioned, is used in combination with CHOP for patients that need chemotherapy, but often times we use the rituximab as a single therapy for patients with lower grade lymphomas. Again, the ones that we might have watched and waited before, now that we have this therapy that does not have many side effects, it is enticing to treat our patients with this immunotherapy earlier on in the course or their disease. The other thing that we do is we actually use this rituximab therapy in some patients after they have finished their chemotherapy in a maintenance setting as well. I just want to say a little bit about radiation therapy because we always approach these diseases from a combined modality point of view. In other words, we have a lymphoma conference where we present all of our new cases and

there are radiation oncologists, pathologists, and medical oncologist that are present at that lymphoma conference and we always explore the possibility as to whether the addition of radiation therapy should be used in an individual lymphoma patient. I will give you an example of where that might be relevant. For instance, we saw a patient in a lymphoma conference today who presented with extensive involvement with a B cell lymphoma but had a very very large mass in the sinus area and we felt that certainly chemotherapy was warranted for that patient, but because of this very large mass we felt that that particular area may need some additional treatment and so the recommendation for that patient was to get radiation therapy following the chemotherapy. It is not unusual for patients with diffuse large B-cell lymphoma or even Hodgkin's disease who have very large masses to have the addition or radiation therapy along with their treatment. So the multimodality approach is very important, and then the other really important aspect of lymphoma therapy is the follow-up for patients. I mentioned that some patients get some treatment in the follow-up periods say with rituximab, other patients actually go on to stem cell transplant. If they have a very aggressive disease, particularly patients with relapse lymphoma, they often times need to have a therapy after they complete their chemotherapy to prevent the disease from coming back. That is an important part of our strategy, but I think the other really important part of our strategy is very careful follow-up for these patients, because if you look at all patients with diffuse large B-cell lymphoma, about half of those patients are going to relapse, and so we need to make sure that we do physical exams and imaging studies such as scans on a regular basis at least for the first couple of years and really educate our patients about what to look for in case there is evidence of a relapse.

Wilson You had mention transplant as a potential option for certain patients, what does transplant mean?

Foss Transplant comes in two different forms, the autologous, which is giving yourself your own cells, and the allogeneic, which means that you get somebody else's cells. When we talk about bone marrow transplant and stem cell transplant, we are really talking about different forms of the same thing, it used to be that we got the cells from the bone marrow by doing multiple different needle sticks into your bone marrow and aspirate out cells, and those would be the bone marrow cells that we would give back to the patient. Now we know that we can mobilize those bone marrow cells into the peripheral blood by using growth factors and other kinds of agents, and so now what we do for a donor is we just stimulate the bone marrow to produce the cells, they go into the blood and the patient comes in to the blood bank and gets hooked up to a machine like they are donating blood. That machine takes the stem cells out of their blood and puts them in a bag, we than freeze them down and give them back to the patient. With an autologous transplant, which we do frequently for some of our aggressive lymphoma patients, we will harvest those stem cells when the patient is in remission, we will then bring patients into the hospital and give them a week of high dose chemotherapy and then give them the stem cells back, and the purpose of that is to allow us to give very very high doses of chemotherapy to get rid of any residual lymphoma cells

21:40 into mp3 file http://yalecancercenter.org/podcast/dec0510-cancer-answers-foss.mp3

that might be left in the body and then give back the patient's own stem cells so that they can reconstitute their bone marrow.

Wilson It does sound very complicated and I would think that treatment recommendations might even be slightly different from hospital to hospital. Are there guidelines that physicians follow, consensus statements that folks tend to look after to try to make sure that recommendations are consistent and as up-to-date as possible?

Foss That is also a very important point to bring up because this issue has been addressed at the national level to establish standards of care for patients with lymphoma, as well as other cancers, and we have now what we call the NCCN Guidelines, which are basically a set of consensus guidelines that direct us as to how we treat various kinds of cancers. This is particularly important for lymphoma because when we look across the board at a lot of our lymphoma subtypes many of these patients are actually curable, so we are dealing with patients who have a curative disease. It is very important then to treat them with the correct therapy in the first line, and so the NCCN Guidelines specifically outline evidence-based approach to treatment for these lymphomas. They basically look at all of the big randomized clinical trials that have been done in the various subtypes of lymphoma and they make recommendations based on what appears to be the most effective, so called standard therapy for the different subtypes. Sometimes, say in the case of T cell lymphoma, for instance, there really are not well established guidelines and so the NCCN will make recommendations, they will say for instance there are four possible treatments that could be used and there is no way of knowing that any one of these is better than the other, but nevertheless there is an algorithm for each one of these diseases identifying what all the possible effective therapies are and what the recommended therapies are if it a situation where there is one that is clearly better than the others.

Wilson Tell us a little bit, Francine, about the different major types of lymphoma, such as Hodgkin's disease, and perhaps what groups of patient that might effect, older patients, younger, non Hodgkin's lymphoma, cutaneous lymphomas, tell us some other details about those diseases?

Foss Hodgkin's lymphoma really has two different age peaks, one of them is young people and the other one is middle-aged people, and Hodgkin's lymphoma is one of the diseases that we feel that we can cure many of the patients and so this is a very important disease to be seen and evaluated in a combined modality setting. Hopefully the slides will be reviewed by a pathologist and make sure that we have the correct subtype of disease, and so for Hodgkin's patients I think the outlook is very good using the conventional treatment strategies that we have. We also have some new approaches for Hodgkin's, new antibodies such as the SGN 35, which is a targeted therapy that specifically binds to a protein on the surface of the cells. For the B-cell lymphomas, I mentioned the low grade and the intermediate or high grade lymphomas, in the intermediate or high grade B

cell lymphomas, again half of these patients are cured with chemotherapy and the addition of radiation therapy in some cases, but half of these patients we expect to cure. It is very important that those patients get treated correctly, that their treatments are given on time and that they are monitored closely in follow-up. In the low grade lymphoma group, that is a disease that tends to occur over a very long period of time, many of these patients will live with their disease for years and years and years. The outlook for these patients is now changing slightly because we do have a number of new therapies that have been developed. I mentioned the rituximab antibody but there also are some other new drug therapies that are developed for patients with low grade lymphoma, and I think in the future that we are going to see the outlook of that disease change and hopefully we will have biological therapies available to treat many of those patients, and then when you get into the T–cell lymphomas, you get into a little bit of a conundrum because again there are two different types of T-cell lymphomas. There are the low grade T-cell lymphomas that primarily are the ones that occur on the skin that you and I are familiar with, the patients with CTCL, and then there are the more aggressive T cell lymphomas that look like B-cell lymphomas that involve lymph nodes, the liver, the spleen, and other organs in the body. In general, the T-cell lymphomas tend to be worse than the B-cell lymphomas. It is very difficult to cure many of these patients with aggressive T-cell lymphoma. That is an area where now we have a lot of research ongoing and interestingly, Lynn, that's been an area where we had a number of new drugs approved by the FDA over the last year. We are now starting to make a little bit of progress in patients with aggressive T-cell lymphoma.

Wilson What are some other side effects of treatments for lymphoma?

Foss Many of these drugs that we use cause side effects like loss of hair, nausea, fatigue, and lowering of blood counts. Many of the conventional chemotherapy drugs, as I mentioned, are given in these cycles every three to four weeks. When you start looking at some of these new biological therapies, the side effect profile is a little bit different. For rituximab, for instance, patients actually do not notice any side effects. For some of the other drugs that we are using, like one of the new drugs that was FDA approved called romidepsin, which is new class of drug called HDAC Inhibitor, the major side effects of this drug are fatigue, nausea, and some diarrhea. So it is completely different than some of the drugs. There is no significant change in your blood count and there is no loss of hair. Another new drug like Treanda that was approved for B cell lymphoma is a drug that does not have any hair loss and so we can now start talking to patient's about some of these options and thinking about lifestyle issues as well as what treatments are effective for some of these lymphomas in the low grade setting, certainly, where patients go on and work and the disease does not effect their life to any significant degree. The choice of these therapies is really important as it fits in with other factors that the patient has at that point in time, and hair loss is one of the things that many of my patients complain about bitterly, it is still an undesirable side effect that we have to deal with with many of our chemotherapy drugs.

28:14 into mp3 file http://yalecancercenter.org/podcast/dec0510-cancer-answers-foss.mp3

Wilson Take Hodgkin's disease, for example, where we have our traditional combined modality therapy treatment, chemotherapy plus radiation, which has been extremely successful for the patients with Hodgkin's, but we worry about side effects and long term side effects, leukemia, new cancers perhaps related to the treatment, and it sounds like there has been some groundbreaking discovery in terms of trying to work on lowering the chemotherapy dose, and lowering the radiation dose, and those program's early data revealed that they look like they are pretty successful. What are your thoughts about that?

Foss That is another area that we're striving to make some in-roads in and that is trying to give the lowest dose of chemotherapy that is going to be effective and eradicate the tumor, and hopefully spare patient's some of those side effects. In Hodgkin's disease there are a number of international studies that are ongoing now, looking at decreasing the number of cycles of chemotherapy that a patient needs to receive, and using tests like PET scan to detect when a patient is having a very good response, so if a PET scan is negative early in the course of the treatment, perhaps that patient needs less cycles of therapy than a patient whose PET scan is still positive say after two cycles of therapy. We are also now looking at using reduced doses of radiation therapy and reducing the felid of radiation that we are treating in order to decrease some of these side effects that patients may have later on.

Wilson This would reduce side effects during the treatment course, and perhaps long-term complications that might not take place for 20 years or 30 years, is that correct.

Foss Exactly, and as a radiation therapist you are aware of the fact that the risk of secondary cancer such as lung cancer or breast cancer in patients who have radiation to the chest is associated to some degree with the amount of radiation that the patient receives.

Dr. Francine Foss is a Professor of Medical Dermatology specializing in the treatment of lymphoma at the Yale School of Medicine. If you have questions for the doctors 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.