Dr. Francine Foss, Understanding Lymphoma March 21, 2010Welcome 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 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 cancer-answers@yale.edu andthe phone number is 1888-234-4YCC. This evening Ed welcomes his co-host Dr. Foss for a conversation about lymphoma. Here is Ed Chu.Chu Francine, thanks so much for being on the other side of the microphone this evening and being here to talk about your favorite subject, which is lymphoma.Foss Thank you Ed, it's a pleasure to be able to talk about lymphoma, particularly today when we have had a flurry of new drugs and a lot of activity in terms of understanding the molecular basis of these diseases.Chu Absolutely and we certainly will get into that, but for our listeners out there, let's start off with a general definition of what lymphoma is.Foss Lymphoma is a malignancy of the white blood cells that comprise the lymph nodes. Lymph nodes, as you know, are part of our immune system in our body. There are multiple lymph nodes in different parts of the body and in those lymph nodes there are different types of cells, particularly T cells and B cells, and then there are some other cells as well. There are three different types of lymphomas all arising from these cells. There are T cell lymphomas, B cell lymphomas, and then Hodgkin's disease.Chu In a show that we did, I think just a week ago, the topic was colorectal cancer and you asked me how I got involved. Let me turn that question around to you and ask how you got involved, what interested you about going into this field of lymphoma research?Foss Well, I have always been interested in blood and diseases involving the blood cells, and when I was back at the National Cancer Institute I got very interested in the T cell lymphoma program. At that time that was one of two or three programs in the Untied States that was focusing on T cell lymphoma and in fact a lot of work that was done in the laboratory that I worked in led to the development of a number of cell lines and led indirectly to the identification of HIV and HTLV-1 in addition, so I got very involved particularly in the potential viral origin of lymphomas at that time.Chu For some background information for our listeners, what age group is typically at risk for developing lymphoma, how common is it?2:45 into mp3 file http://www.yalecancercenter.org/podcast/mar2110-cancer-answers-foss.mp3Foss It's interesting, and I don't think most people out there are aware of this, but if you look at the SEER data looking at the incidence of cancers in the United States, non-Hodgkin's lymphoma actually is the fifth most common cancer behind the solid tumors like lung, colon, and bladder and the number of new cases in the United States is actually increasing. It's 74,490 cases as of last year and that's gone up at least 10,000 from 2009. In addition, about a quarter of these patients, or 20,000 patients, will go on to die every year of non-Hodgkin's lymphoma. The median age is 67, although the disease certainly does occur in very young people, in children all the way up to the elderly.Chu Francine, what do we know about the risk factors for developing lymphoma?Foss That's an interesting question Ed, and it really

requires a fairly long answer, but I can summarize it by telling you that for many patients the risk is unknown. Most cases of non-Hodgkin's lymphoma occur sporadically, however, we do know that certain populations are at high risk and that includes people who are immuno compromised for some reason, particularly because they have had an organ transplant, like kidney transplant or liver transplant and they have auto-immune diseases that require them to take immuno suppressive medications. Also people who are infected with HIV or who have the HTLV-1 virus and we now know that people who have hepatitis C virus are also at an increased risk. In addition, we have the EBV virus that causes Mono that we are all exposed to as young children and that can be a risk. Recently we found an increased incidence of gastric cancers, lymphomas of the stomach, in people who have H. pylori, which is essentially an infection involving the stomach lining. And then finally, we always worry about occupational exposures because there has been a connection between benzene, or chemicals, and Leukemia, and we also have seen with the Agent Orange exposure during the Vietnam War, an increase in the incidence of lymphomas in these populations. We then extrapolated that to look at people say in the Midwest where they are exposed to a lot of herbicides and pesticides on farms and we have seen an increased risk in that population as well.Chu There really are a wide number of different risks factors.Foss And one of the interesting things that Yale Cancer Center has been pursuing over the last 10 or 15 years is looking at these epidemiologic factors, and in fact, we have a very active group here that performs studies looking at all of these different factors and one of the things that actually came up, as you may remember, is the connection between hair dye and the incidence of B cell lymphomas.Chu Francine, you mentioned a moment ago that we are seeing an increased incidence of lymphoma, do we know why that's happening?5:49 into mp3 file http://www.yalecancercenter.org/podcast/mar2110-cancer-answers-foss.mp3Foss I think there are a number of reasons for that, one of which is that we are using more of these immuno suppressive medications, we are doing more organ transplant nowadays. In addition, there are a lot of people out there that are infected with Hepatitis C, and with respect to the occupational exposures it's really hard to get your hands around that. Many people when you question them don't really know what they are exposed to at work, but I think obviously with increased pollution levels in the environment in general, certainly we are all exposed to more chemicals that we don't even know about.Chu Lymphomas are a very broad term, there are obviously specific subsets of lymphoma. Can you tell us a little bit about that?Foss There are different subsets based on the cell types, so I said B cell, T cell, and Hodgkin's. That's a broad way to categorizes lymphomas, but then within each of those different subsets there are different subsets, so within the B cell lymphomas there are a group of patients that have what we call low grade or indolent lymphoma that can do very well for a long period of time, often times without treatment, or if they do get treatments, it is very low level, nontoxic types of approaches. On the flip side, there are lymphomas that are very aggressive. In the T-cell group there are the cutaneous lymphomas that are indolent, again low grade and slowly progressive, and then there are more aggressive T cell lymphomas.

And then within Hodgkin's disease there are a number of different subtypes that have different outcomes. Primarily with Hodgkin's there are very early stage patients that do very well with localized therapy or short course chemotherapy, and then there are the more advanced stage patients that require more aggressive approaches.Chu How can one differentiate between these different subtypes of lymphomas?Foss The histology and the pathology is critical in the diagnosis of lymphoma. All the action is really under the microscope and we depend on our colleagues in hematopathology to look at this tissue and do a number of different special stains looking at specific markers. Over the last 5 or 6 years we have come a long way in identifying and subtyping lymphomas based on the identification of specific markers that identify a specific type, such as mantle cell lymphoma, which is identified by the expression of the Cyclin D1 gene. In addition, we have various chromosomal abnormalities that we can detect that help us to subtype these different types of lymphomas.Chu Are there any blood tests that can help the diagnosis of a particular type of lymphoma?Foss The blood test does not necessarily help us in the diagnosis, but it can actually detect the presence of lymphoma cells in the blood. So, while you think about lymphoma as occurring in the lymph nodes primarily, these cells travel around from one lymph node to other so they essentially all get in the blood at one point or another, and using very sensitive techniques like flow cytometry and8:53 into mp3 file http://www.yalecancercenter.org/podcast/mar2110-cancer-answers-foss.mp3 gene rearrangement studies we can detect these small populations of cells. In certain types of lymphoma, as they become more advanced, we see more of these lymphoma cells in the blood and I will also mention that they can get into the liver, spleen, and the bone marrow and the other parts of the body as well.Chu All of us at some time or another have felt swollen lymph glands that get tender. When does one have to begin to worry that this is more than an infection and something more serious?Foss That's one of the more common problems that the primary care doctor faces, is patients coming in with swollen lymph nodes who may or may not have symptoms. Clearly if you have a runny nose or a sore throat and you have lymph nodes in your neck, or if you have a rash on your foot and you have a groin lymph node, it is easy to explain why that lymph node is there. In many cases there will be a history, however, there are patients that do show up with a lymph node without any evidence of an infection, and in some of those cases there could have been an occult infection that was missed and the lymph node will resolve over time, but in other cases one has to worry about that node and so generally what I tell people is if you have a lymph node that's been there for a month and it's not getting any better, at least get it checked out.Chu Are there any other symptoms that are typically associated with lymphoma?Foss Just like with other kinds of cancers, many of our patients with lymphoma come in without symptoms, particularly patients with low grade lymphomas; however, when patients do get sick with lymphoma the kind of symptoms that they experience could be things like fevers and night sweats, which are drenching sweats at night. Patients could be fatigued related to the lymphoma or to anemia that can develop from the lymphoma. Patients can have bone pain, they can have pain in their organs,

and they can just feel over all run down and sick, but like I said, many of our patients come in asymptomatic because they noticed a lymph node that did not go away.Chu If anyone should experience any of these symptoms that you just mentioned, what should they then do?Foss That's kind of a grey area again for the primary care doctor because many of those symptoms could be seen in other conditions. Patients who are fatigued, run down, or have other illnesses for instance, could have those symptoms. And so what needs to be done I think is a good physical exam and a blood test. A blood test does not always pick up lymphoma, but there can be some hints there, for instance if the CBC, the white count, the red count, or the platelets show abnormalities that can certainly be an indicator, and if you look at the chemistries, sometimes a marker called LDH is elevated in people who have lymphoma, but I just want to let our listeners11:47 into mp3 file http://www.yalecancercenter.org/podcast/mar2110-cancer-answers-foss.mp3know that a number of patients with early stage lymphoma come in with a completely normal set of blood tests.Chu Should individuals seek out medical attention with their primary care physician, general internist, when would they come to see a specialist like yourself?Foss We are really depending on the general internist and the primary care doctors to pick up these lymph nodes or symptoms that might be suggestive of lymphoma, and often times patients will get sent to a surgeon or a needle biopsy of the lymph node or a blood test will show something abnormal before they come to see us, however, as a lymphoma doctor, I will get patients directly sent to me by a primary care doctor who has found a lymph node and will send the patient to us to pursue the workup to make the decisions about what kind of test needs to be done, for instance a needle biopsies versus excisional biopsy of that node.Chu We have talked about all of the different risk factors and there are many, but what do you know about the genetics of lymphomas?Foss There are certain family syndromes where lymphomas can occur, and interestingly in some of these families lymphomas occur with other solid tumors, and that's primarily the situation that we have seen in our patients. There are very few patients that have a genetic predisposition. There are some families or ethnic groups that have a higher instance of lymphoma and that includes people from Japan or the Caribbean, primarily because they may be infected with HTLV-1.Chu At this point we are going to take a short break for a medical minute. Please stay tuned to learn more information about the evaluation and treatment of lymphoma with my co-host and guest Dr. Francine Foss.Chu Welcome back to Yale Cancer Center Answers. This is Dr. Ed Chu and I am here in the studio14:32 into mp3 file http://www.yalecancercenter.org/podcast/mar2110-cancer-answers-foss.mp3 this evening with my co-host and friend Dr. Francine Foss who this evening is our guest expert discussing the evaluation and treatment of lymphomas. Francine, let's talk a little bit about once an individual is given the diagnosis of lymphoma, how does one evaluate to see what the extent of the disease is?Foss The first thing we would like to do is to know whether the lymphoma is localized or has spread to other areas of the body. There are a couple of ways to do that. One of which is to get a CAT scan, which is the traditional test, but more recently we have started using PET scans because

PET scans are a different kind of imaging that actually is enhanced in areas that are metabolically active and lymphomas are particularly sensitive to this technology. So, if we can get a PET scan along with the CAT scan, which is called a CT PET scan, that's our preferred method of imaging. In addition, we would like to, in most of our patients, also get a bone marrow biopsy just to see whether the lymphoma involves the bone marrow, and that sounds pretty scary to patients but it's actually a very simple procedure. We do it right in the office. We now mark the area that we are going to put the needle in and then we put small needles in and we take a sample of the bone marrow.Chu I am curious, how often does lymphoma spread to the bone marrow? Or does it depend on the particular subset of lymphoma that we are dealing with?Foss That really depends on the subtype of lymphoma and for patients with say limited stage Hodgkin's disease, it's very rare, whereas for patients with follicular lymphoma, it's very common.Chu Once a patient has been staged, then how do you go through the treatment planning and recommendation for the particular type of treatment?Foss The treatment planing is highly dependent obviously on the type of lymphoma; however, we can generalize to some degree. If we look at say low grade lymphomas, there are about 7 or 8 different subtypes within that category, but essentially we treat them all the same way and likewise with the diffuse large B cell lymphoma, it depends on stage. In a very small number of cases, patient may only get radiation if they have localized lymph nodes and nothing else. But most of our patients now are getting systemic therapy, and we are very fortunate, particularly in B cell lymphomas, that we have the monoclonal antibody Rituximab, which is a first-line therapy for pretty much all of our patients with B cell lymphoma. Some of those patients with more advanced disease may get the antibody with chemotherapy, but many of our early stage patients may get the antibody by itself as a therapy.Chu This antibody Rituximab, what is it targeting?Foss This antibody targets CD 20, which is a protein on the surface of the B cell and is expressed pretty17:28 into mp3 file http://www.yalecancercenter.org/podcast/mar2110-cancer-answers-foss.mp3 much on all B cell lymphomas, so it's a drug that we can use across a wide range of different types of B cell lymphoma.Chu What's pretty remarkable about this antibiotic treatment compared to some other treatments in my own disease, colorectal cancer, is it really is specific for this CD-20 positive lymphoma.Foss That's right. One of the side effects of the antibody that most patient don't even notice is that it does decrease the normal B cells to some degree, but they pretty much rebound and for most patients there is no sequela in terms of increase in infections, so that is one thing you do need to watch out for.Chu Now again, do you use this antibody alone or in combination with more traditional chemotherapy? Foss There have been a lot of studies done in the United States and other countries looking at large groups of patients with B cell lymphoma showing that the combination of this antibody with chemotherapy is superior to the use of chemotherapy alone. Whereas we used to give a combination called CVP for patients with follicular lymphoma, now we are giving R-CVP and for patients with the diffuse large B cell lymphoma we used to give just CHOP, and now

we are using Rituximab with the CHOP. The other role of this antibody is in the maintenance settings, so patients who have had chemotherapy may then just get an antibody to try to keep them in remission.Chu Are we really impacting then on the cure rates of patients with lymphomas being treated with this antibody?Foss Ed that's a really interesting question and if you look say at follicular lymphoma, we have very good data going back 30 or 40 years looking at the overall survival of patients with this disease, and really we have not made much impact in that survival until very recently, and when Rituximab was approved in the mid 1990s, we started to see a plateau on that survival curve, so it looks like perhaps the use of Rituximab, and perhaps other new drugs that we have for treating lymphoma, are now starting to make an impact on the overall survival of these patients and that's really the important thing for the patient to know is that we are now using therapies that perhaps can cure their disease for the long term.Chu Let's talk about some of these newer drugs because it really is remarkable, the advances that have been made just even within last 3-5 years, and you have been very actively involved in development of many of these drugs, so take us through some of those newer agents.Foss I mentioned Rituximab, the CD 20 antibody, and there has also been the combination of that20:12 into mp3 file http://www.yalecancercenter.org/podcast/mar2110-cancer-answers-foss.mp3 antibody with radioactivity, and those two drugs are called Zevalin and Bexxar, radiolabeled antibodies, and those are also being used extensively in patients with B cell lymphoma. In addition, we have another antibody directed at CD 20 ofatumumab and that antibody was recently FDA approved for patients with CLL, but is also being used in clinical trials for patients with B cell lymphoma, and has activity in patients that have been refractory or relapse after the Rituximab, so I think that's an important addition. If we look at some of the other kinds of lymphoma, the T cell lymphomas, which are particularly difficult to treat and generally have a worse prognosis, we have a number of drugs that have been FDA approved. About 10 years ago the molecule ONTAK was approved and that specifically targets the Interleukin 2 receptor, which is expressed on many T cell lymphomas. More recently, this year we have been fortunate that the FDA approved two new drugs for the treatment of T cell lymphoma, one of those drugs is called Pralatrexate or Folotyn, and that drug is actually a derivative of a very old drug that we had been using for a long time called Methotrexate. This drug is a drug that is particularly active in patients with aggressive peripheral T cell lymphoma, but importantly it is also now being looked at in other kinds of lymphoma as well. The other drug is a whole new class of drugs called histone deacetylase inhibitors, so the drug Romidepsin or Istodax was approved for patients with cutaneous T cell lymphoma, however, this drug again is also being used in patients with aggressive T cell lymphomas as well as multiple myeloma and B cell lymphoma. I think we are going to learn more about these histone deacetylase inhibitors and how they combine with other chemotherapies, not only in lymphoma, but also in other solid tumors. It's very exciting now to have two new drugs approved in one year.Chu It really is very exciting and remarkable. Do you think the reason we have seen these advances is that we are finally seeing the payoff from

all the years of basic research trying to understand what turns on or turns off these various lymphomas?Foss That's a very important point Ed, and that is that nothing new happens in the clinic unless a lot of work gets done behind the scenes in the basic science laboratory, understanding the molecular biology of these diseases, and we have come a long way, as I have mentioned, in identifying specific proteins that we can target on these cells, were looking at specific pathways that are activated to which we could direct targeted therapies. I want to mention one of those in particular, if we look at a certain subset of T cell lymphomas, the ALK-positive anaplastic large cell lymphomas, they express this protein called ALK. There has been the development of an inhibitor of ALK that interestingly is in clinical trials in lung cancer and will also be used in patients with ALK-positive T cell lymphoma.Chu Francine, you have been very actively involved in developing new agents, new treatment regimens, tell us a little bit about what's going on with your program at Yale Cancer Center.23:35 into mp3 file http://www.yalecancercenter.org/podcast/mar2110-cancer-answers-foss.mp3Foss Our program involves trying to get some of these new drugs into patients with lymphoma and also trying to look at some of the combinations that we can use that would capitalize on synergistic interactions in targeting pathways that are important in these patients. We are very interested in the histone deacetylase inhibitors and looking at how we can combine them with other agents that affect the transcription of genes, and so we have a combination of a drug called Doxil with a histone deacetylase inhibitors called vorinostat, and that's open for patients with all types of lymphoma. Interestingly, we have seen some very significant activity in Hodgkin's disease, which we would not have expected, and so that's an example of learning something new about your drug combination by opening up your trial to a number of different types of patients. In addition, we are looking at some of the novel histone deacetylase inhibitors and we have also done a clinical trial combining the drug ONTAK with CHOP as a first-line therapy in patients with aggressive T cell lymphoma. We have actually shown that combination works better than the CHOP alone and that perhaps could be a major advance in the treatment of some of these patients with aggressive T cell lymphomas. We are also looking at some novel phase 1 molecules and trying on incorporate them into treatment of patients with relapse B cell lymphoma, in particular, because those patients, if they don't go to bone marrow transplant, don't have really good options.Chu We have talked a lot about chemotherapy and these new targeted agents, and you just mentioned bone marrow transplantation. When would one consider recommending transplantation to a patient with lymphoma?Foss Bone marrow transplant for lymphoma is done under very defined conditions and a lot of this has been defined based on the medical literature and also the NCCN guidelines which direct us in terms of what the standards of care are for different diseases. So, for patients with diffuse large B cell lymphoma, generally speaking, at least half of those patients will go into remission with chemotherapy and never relapse, however, if they do relapse and they get additional chemotherapy, than a bone marrow transplant for consolidation is the recommendation at that point, or if the patient has failed their first-line therapy, and we give

them a consolidation therapy, then we may consider moving them to a transplant. For patients with a follicular lymphoma often times those patients can go on to many other therapies and transplant really is not required or necessary until they have had multiple therapies and they have shown that their disease is less responsive and we really need to do something to consolidate their response. The autologous transplant is high dose chemotherapy to try to consolidate a response in a patient with lymphoma where as an allogeneic transplant involves getting cells from another person and therefore getting an immune effect, so up-regulating your own bodies chance of responding to a cancer by giving yourself new immune cells from a different person. That's a whole difference strategy and we do use that strategy in patients particularly with relapsed and refractory lymphomas, people that have very difficult diseases. With respect to the T cell lymphomas, often times we need to go to that allogeneic transplant first because we know that T cell lymphomas tend not to do as well with the27:09 into mp3 file http://www.yalecancercenter.org/podcast/mar2110-cancer-answers-foss.mp3autologous transplant.Chu What are some of the complications that are typically associated with say the allogeneic transplant?Foss I want to mention to our listeners when we talk about the word transplant people tend to put autologous and allogeneic together, and it's important to separate the two because autologous transplant is really very safe and the chance of dying from an autologous transplant is really very low, it's probably one percent or less. Whereas an allogeneic transplant, as I mentioned, involves getting cells from a donor, from somebody else, one of the risks of that is that donor cells could recognize proteins in your body that are slightly different and they could attack your body and that process is called graft-versus-host disease. When we do an allogeneic transplant, we hope that those new cells are fighting against the tumor cells because they recognize the tumor cells as being foreign but we would like to diminish the chance of those cells fighting against the body and generating graft- versus-host disease.Chu Francine, you have been very actively involved in trying to develop novel strategies to reduce the incidence of graft-versus-host disease, but at the same time enhance the tumor effects, can you quickly tell us about that?Foss Based on some work that we have done in the laboratory, we have shown that the use of photopheresis treatment prior to the conditioning regimen for allogeneic transplant decreases the chance of graft-versus-host disease, and in fact, we have had a clinical trial that has been ongoing here at Yale, but also in other centers, to look at the use of photophoresis in this setting. And particularly for lymphoma patients we have seen very good results and by decreasing the chance of graft-versus-host disease, we have been able to transplant patients successfully and had a graft- versus-tumor effect such that their lymphoma is in remission after the transplant, so I think this is a major step forward in our ability to transplant more patients with lymphoma.Chu Francine, it's amazing. The time has quickly gone by. It has been great having you on the show and hearing about all of the wonderful advances that are taking place in the treatment of lymphoma.Foss Thank you Ed, it has been a pleasure to be here to talk with you tonight.Chu Until next week, this is Dr. Ed Chu from Yale Cancer Center wishing you a safe and healthy week.If you have questions

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