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answers

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Advances in Lymphoma

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Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and an internationally known expert on colorectal cancer. Dr. Miller is a Medical Oncologist and the Director of the Connecticut Challenge Survivorship Clinic. If you would like to join the discussion, you can e-mail your questions directly to the doctors at canceranswers@yale.edu. You can also call 1-888-234-4YCC. This evening, Dr. Chu and Dr. Miller will be talking about lymphoma. They are joined by Dr. Francine Foss a Professor of Medical Oncology and co-Director of Yale Cancer Center Leukemia, Lymphoma and Myeloma Program.

- Miller Francine, I want to start with a very basic question. When people hear the word cancer they tend to think of lung cancer, breast cancer and colon cancer; however, those differ from lymphomas. What makes lymphoma different and special?
- Foss Lymphoma is a disease of the white blood cells or the lymph nodes. So unlike with colon cancer, breast cancer or lung cancer, often times the patient does not know that they have lymphoma because some of these lymph nodes are internal. In some cases, patients have lymphoma for a long time and are only diagnosed when they go to the doctor for another reason.
- Miller What are the different types of lymphoma?
- Foss There are 2 major categories of lymphoma. There is Hodgkin's lymphoma and non-Hodgkin's lymphoma. Hodgkin's lymphoma comprises about 5000 cases per year in the United States. Non-Hodgkin's lymphoma is by far the more prevalent type of lymphoma. In non-Hodgkin's we have both B cell and T cell. Within each one of those categories there are a whole bunch of other subcategories of disease.
- Chu It is very complicated and unfortunately many people out there hear lymphoma and they lump everything all together. They are very different entities and treatment approaches can also be quite different depending upon the specific lymphoma.
- Foss That is right, the treatment depends on the specific subtype of lymphoma, how far that lymphoma has spread and what parts of the body are involved. There are other features of lymphoma as well that we take into consideration. Often times a treatment that has been recommended for one patient, may not be relevant to another patient.
- Miller Sometimes people have heard in the public that a cancer went to the lymph nodes and they think it is a very bad thing. Does that same kind of rule apply to lymphoma in terms of prognosis? Does involvement of lymph nodes mean that it is a particularly bad disease?

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- Foss No, and I think there is a lot of confusion on that point. As you know many lymphomas occur in lymph nodes, but they can also occur in other parts of the body too; somebody with lymphoma in fact may have a lesion in the breast or the lung. There is a lot of confusion because when you think about solid tumors like lung cancer, people do not do so well. You have to be very careful to separate that from lymphoma. Lymphoma is a curable disease in almost half of patients who have it.
- Chu That really is an important point to emphasize for listeners out there, that lymphoma is treatable and potentially curable even if it is wide spread throughout the body. This is in sharp contrast to say solid tumors, which are treatable but may not be as curable as the lymphomas.
- Foss That is right. It is important for the patient to keep that in mind, and even if your doctor tells you that you have advanced stage lymphoma, often times you will respond very nicely to chemotherapy and possibly radiation therapy as well. Many of our patient's become long-term survivors.
- Miller Do we have any idea what causes lymphoma?
- Foss It is unclear but there are a couple of studies which suggest that lymphoma may be associated with various occupational exposures; exposures to chemicals. There are lots of pesticides and chemicals in our environment and in fact if you look at the overall incidences of lymphomas, they have increased over the last 10 or 15 years. That may be associated with pollution, increased radiation due to loss of the ozone layer and other factors that we have not identified. There are some lymphomas that are associated with viruses, but those are very rare, and there are also some lymphomas that run in families.
- Miller Along those lines, is it a truth or a myth that if a parent has lymphoma that their son or daughter is at very high risk?
- Foss That's a myth for most patients. The chance of you having a familial lymphoma is very, very low.
- Miller Truth or myth, if someone is exposed to the mono virus, the Epstein-Barr virus, they are at very high risk of developing lymphoma?
- Foss That is another myth. The mono virus can be associated with lymphoma but the number of cases again is very small.
- Chu How about the HIV virus?
- Foss The HIV virus predisposes patients to a lot of different diseases and because it

suppresses the immune system, it may cause those patients to have higher incidences of developing diseases.

- Chu There is also an increased risk of developing lymphoma in patients who have undergone transplantation of the liver, kidneys or other organs. That is partially due to the fact that we have developed such good drugs that suppress the immune system to cause those organs not to be rejected. But they are also suppressing the part of the immune system that surveys and gets rid of malignant cells. In that case there is an increased incidence of different types of lymphomas.
- Miller Let me ask you for your opinion on something. Some people say that all of us will probably have cancer at one time or another but our immune system fights it off. What is your view of that in regards to lymphoma?
- Foss That is a very good point and something that we're just starting to recognize now, and that is the value of our immune system in terms of surveying and scavenging cells that may have undergone various types of mutations. This is occurring all the time in our body in multiple places, related to multiple events. What happens is that our immune cells, specifically the T cells, are killing these cells that they recognize as foreign that have undergone mutations. In any situation where the immune system is suppressed, be it from medications if you have had a kidney transplant, or if you have HIV, the immune system is not working well enough to go out and scavenge. In that situation you have a higher risk of having one of these malignant cells grow large enough to develop a tumor or cancer.
- Chu What are the symptoms associated with lymphoma and non-Hodgkin's lymphoma?
- Foss One of the tricky things about lymphoma is that many patients actually have no symptoms. They may be diagnosed going to the doctor for another reason. The doctor finds a lymph node on a physical exam or perhaps finds something abnormal in their blood work. Other symptoms could be swelling of lymph nodes, fatigue or weakness or developing night sweats. Generally speaking a lot of our patients do not have many symptoms when they come in.
- Miller If a person notices large lymph nodes, what are some of the possibilities that it could be besides lymphoma?
- Foss It really depends on the patient and the situation. If you examine your neck you can probably feel a couple of little bumps. This is your normal immune system working. Lymph nodes will get large if exposed to bacteria or viruses that we have all experienced at one time. The thing that tips us off that there is a problem is if there is a lymph node that is enlarging overtime at a rate that we think is rapid and perhaps not related to an infection. In some cases these lymph nodes can pop

up very quickly and so often times what the doctor will do is examine you and feel the lymph nodes. If it is not significantly enlarged they may watch you for a couple of weeks and see what happens. Then, if the doctor is convinced that this isn't just a simple infection, they may recommend that you have lymph node biopsy.

Chu If someone has a lymph node that is tender to the touch, is that more likely to be a cancer or a benign cause?

Foss That is more likely to be benign. Most tender lymph nodes are tender because you have an infection or an inflammation.

Miller I remember in my own practice of oncology in the community seeing people who had a big node that we suspected was lymphoma, but then finding out that it was not; that was very gratifying.

Foss Often times an oncologist does not have that experience of seeing a patient that does not have cancer.

Miller Right.

Foss It is important for patients with enlarged lymph nodes, if they do have biopsy, to keep an open mind until they get their final path report.

Miller What tests do patients typically have? There are so many different kinds of tests available; PET scan and MRIs. Also, what do you see as the most valuable staging test?

Foss That is actually changing now. It used to be that we got a CAT scan on everybody and the CAT scan showed whether the lymph nodes were enlarged or not, but it did not necessary tell us whether those lymph nodes were involved with lymphoma. Now we have a new imaging technique call PET scan, which involves a radiolabeled element that actually enhances in lymph nodes that are involved with lymphoma. We can take a picture and see all of the lymph nodes and only the ones that are involved with lymphoma light up on the PET scan. We often times do a CAT scan with the PET scan and put all that information together to stage the patient. I will say that the PET takes a little bit more time and you do have to be fasting so it is a little bit different than just getting a CAT scan. That is the direction that where going in lymphoma to stage patients initially, and then after treatment as well.

Chu Any other diagnostic tests that need to be done as part of the evaluation process in addition to the PET scan or the CT scan?

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- Foss In addition to getting the PET scan, we do routine blood work and in many incidences we will get a bone marrow biopsy. That involves numbing up an area on the back and putting a very small needle in to aspirate some of the bone marrow. The reason we do that is to see whether the lymphoma has spread to the bone marrow. It is not uncommon with certain types of non-Hodgkin's lymphoma to have bone marrow involvement.
- Miller Typically people think of cancer and they think of a disease that changes rapidly. On the other hand, in lymphoma, there is a whole interest in the lymphomas. What is that mean to you as a clinician?
- Foss About a third of the lymphomas we see fall into the indolent lymphoma category. What that means is that the lymphoma is growing very slowly. In fact, we did a study about 20 years ago at the National Cancer Institute where we looked at the behavior of the indolent lymphoma. We found that you could actually watch and wait and not even treat patients, and the lymphoma would just grow very slowly over time. It did not make any difference whether we gave chemotherapy. It is important, when you have a diagnosis of lymphoma, to talk to your doctor about what type of lymphoma you have. If you do have indolent lymphoma you need to ask a lot of questions because there are new treatments out there now for endolymph lymphoma. It used to be that there was only chemotherapy, and in that case we knew that giving chemotherapy versus watch and wait really did not make any difference, but now that we have new drugs like rituximab, which is a monoclonal antibody and has very little toxicity in terms of side effects, we are starting to rethink our strategy for approaching patients with low-grade lymphoma. Perhaps we could use this monoclonal antibody and give it on an intermittent basis which might keep the lymphoma under control for a longer period of time.
- Chu Are there are any situations in which you might be more inclined to treat with Rituxan and/or other treatments in patients who have this low-grade endolymph non-Hodgkin lymphoma?
- Foss The reasons that we treat low-grade lymphomas are based on whether or not the patient has any symptoms. For instance if the lymph nodes are enlarged, they might be pushing on an organ, if there is extensive involvement in the bone marrow the bone marrow will not make normal cells, or if the patient has symptoms like fatigue or weakness related to their lymphoma, that would be an indication to treat those patients.
- Miller The kinds of therapies that you call monoclonal antibodies, do they have a lot of side effects? Is it similar to chemotherapy?
- Foss The antibody is basically a protein substance that your body makes and the

monoclonal antibody is directed against a specific protein on the surface of the tumor cell. These antibodies are injected and they go directly to the tumor site and affect the tumor cells so that they eventually inhibit the tumor cell from growing. Because these are proteins, there might be an initial reaction when you get the infusion, however, we can manage that with steroids and other medications. Generally speaking, after 1 or 2 infusions the antibody infusions are tolerated very well. The patient does not even really know they are getting treatment. There are no symptoms like nausea, vomiting, hair loss or anything else that you attribute to chemotherapy.

Chu The beauty of this kind of treatment is that it is like a targeted therapy in that it targets specific path processes of the lymphoma cell.

Foss This is what we call a biological therapy, which means that we were directly trying to attack the tumor cell with a very specific agent as opposed to chemotherapy. Chemotherapy is basically a chemical that goes into your body and affects not only the tumor cells, but normal healthy cells as well.

Miller We would like to remind you to e-mail your questions to us at canceranswers@yale.edu. We are going to take a short break for a medical minute. Please stay tuned to learn more information from Dr. Francine Foss from the Yale Cancer Center.

Medical Minute

It is estimated that over 2 million men in the US are currently living with prostate cancer. One in six American men will develop prostate cancer in the course of his lifetime. Yet major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from prostate cancer. Screening for this disease can be performed quickly and easily on the physician's office using 2 simple tests, a physical exam and a blood test with screening, early detecting and a healthy lifestyle prostate cancer can be defected. Clinical trials are currently underway federally designated comprehensive cancer centers like the one at Yale. The Patients enrolled in these trials are given access to experimental medicines, which have not yet been approved by the Food and Drug Administration.

This has been a medical minute. More information available at www.yalecancercenter.org

Miller Welcome back to Yale Cancer Answers, this is Dr. Ken Miller, and I am here with my co-host Dr. Ed Chu, and Dr. Francine Foss discussing the latest treatment options for patients with lymphoma. Francine, we were just talking about patients with low-grade lymphoma. Can you think of an example of someone you have treated who is sort of a typical patient that you would see?

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- Foss Yes, I like to talk about a lady that I am treating right now who is a very active woman. She works both in New York and here in Connecticut, and travels extensively. She came in with enlarged lymph nodes and no other symptoms. She was diagnosed with low-grade lymphoma. When we looked at her PET scan we saw that she had multiple areas of involvement and that some of these nodes were a little bit bigger than I was comfortable with in terms of watching and waiting versus treating her. We had extensive discussions about treatment and decided that she would receive rituximab. She received 4 doses of the monoclonal antibody. That was 18 months ago. Since then we have done serial PET scans every 3 or 4 months and she has had really no change in her disease. She is very functional, working full-time and is an example of what can happen with patients with low-grade lymphoma. She is going about her normal life but she knows that at some point if her PET scan shows that there are nodes enlarging again, she will be eligible to receive another 4 doses of the rituximab and that may give her a remission that lasts 6 months, a year or 2 years.
- Chu Is there any situation, say for instance for this patient, where you would consider chemotherapy?
- Foss This patient is cognizant of the potential complications of chemotherapy and would like to delay it as long as possible. There is no reason to give chemotherapy unless the monoclonal antibody treatment doesn't work. At this point there are a number of other options besides chemotherapy. There is a radiolabeled monoclonal antibody that directly takes radioactivity to the side of the tumor that may be an option for patients. The advantage of this is that it is a one-shot deal. You come in, you get your dose of radiolabeled antibody and that stays in your systems for a long time. If we got to the point where we were talking about chemotherapy I certainly would discuss monoclonal antibodies, other monoclonal antibodies, radiolabeled antibodies and potentially other biological therapies as well.
- Miller There are other types of non-Hodgkin's lymphoma that you brought up earlier. Can you tell us about the other types where you would consider chemotherapy early on.
- Foss There are patients with what we call diffuse large cell lymphoma, which is a B-cell lymphoma that grows rapidly. In that case, we would institute chemotherapy right away and interestingly, we would also use the monoclonal antibody rituximab with chemotherapy because we know from multiple studies that it makes the chemotherapy work better. In the case of these large cell lymphoma patients, about half will actually be cured with 6 cycles of chemotherapy. We also know that if patients relapse after chemotherapy we have a very high chance of curing them with more chemotherapy and an autologous bone marrow

transplant, which means that we take cells from the patient and freeze them. We then give them high doses of chemotherapy and put their cells back.

- Miller What is the theory underlying that? Why does a bone marrow transplant work?
- Foss In this case, bone marrow transplant is a way of allowing us to give very high doses of chemotherapy that might eradicate the patient's own bone marrow function. What we do is stimulate the bone marrow in advance and make it produce lots of stem cells. We then take those stem cells out of the blood and then give the patient the very high doses of chemotherapy. When their blood count goes down, we give them back their stem cells to rescue their bone marrow.
- Chu The reason why we can give high doses of chemotherapy and then followup with a transplant is that we know that the lymphoma cells and those tumors specifically are very sensitive to chemotherapy.
- Foss That is right and in fact, if a patient does not respond to the conventional doses of chemotherapy, that does not mean that they are not going to respond when they get these high dose regimens.
- Chu A common question that is asked of me sometimes in patients who have metastatic colon cancer or other GI cancers, is that they have gone through all of the usual treatments and they want to know if they are eligible for a transplant, because they hear that transplant are so successful for cancer in general. But for the listeners out there, do not be confused. The transplant setting is really only applicable for those tumors that are really sensitive to chemotherapy and unfortunately solid tumors like colon cancer do not fall in that category.
- Miller The other kind of transplant where it comes from a donor is allogeneic transplant. How is that different and what are the forces that are working to help the patient?
- Foss Allogeneic transplant involves getting cells from somebody else. By definition it means that new cells are going to come into your body. Those cells may potentially reject you body. What happens with a donor is that the donor cells may recognize proteins on the surface of the patient's cells and institute a process called graft-versus-host disease, what that means is that there may be a skin rash, elevation of liver function test as well as the development of diarrhea. This is the major complication when we do this kind of transplant. Those new donor cells are also going to recognize patient's tumor cells as being foreign and that is really the goal of that kind of transplant. The goal is to give the patient a new immune system, T-cells from a donor that will recognize their lymphoma cells wherever they are hiding in the body and will kill those cells. That is what we call immunotherapy.

- Chu Francine, in addition to being an expert in lymphomas, you also are one of the world's leading experts in a particular type of lymphoma called cutaneous T-cell lymphoma. Can you tell our listeners out there what that lymphoma is and some treatment strategies that you have played a role in?
- Foss This is a very disfiguring disease that predominantly presents in the skin. Patients will develop skin rashes or tumors, and in some case they can develop ulcerations on the skin. This disease does not just involve the skin, often times it is in the blood and the lymph nodes as well. This can be a very, very difficult disease to treat because, first of all, the cells are not as sensitive to chemotherapy as the cells in say B-cell lymphoma, but also because there are lots of symptoms. Many patients have involvement of their face or areas of their skin that are visible to other people, patients can develop frequent infections and have bad itching and other complications from this disease.
- Miller You have done some fascinating work on interleukin 2 fused with a toxin, can you tell us more about that.
- Foss What we have done is we have taken the interleukin 2 gene and we have hooked it up to diphtheria toxin to create what we call a recombinant fusion protein. What this molecule does is the actually seeks cells that have the interleukin 2 receptor. It binds to those cells and it introduces the toxins specifically into those cells so this is another kind of what we call targeted therapy just like the rituximab monoclonal antibody specifically binds only to a certain receptor on the cell. The fusion protein recognizes only the cells that have that receptor and only introduces the toxin into those cells. So, this is again another very selective way to kill these kinds of T-cells lymphomas.
- Chu You have also been involved in two other new therapies recently approved for the treatment of CTCL.
- Foss Another interesting therapy that was approved this year is vorinostat; which is what we call an HDAC inhibitor. This drug was approved for patients with advanced CTCL, but the important thing about it for all cancer patients is that this drug has activity in a number of different types of tumors. We are just now starting to understand how this type of therapy works. In fact there are a whole bunch of HDAC inhibitors that are now in clinical trials.
- Miller What is HDAC?
- Foss HDAC stands from Histone Deacetylase Inhibitors. Basically these are drugs that attack your DNA and modify your DNA to induce various genes that help tumor cells to die. This is a whole new strategy to treat cancer.

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- Chu Can you tell us about other clinical trails that you and your research team here at Yale Cancer Center are actively involved in?
- Foss There are a number of clinical trials ongoing for patients with lymphoma, including investigations of some of these new drugs such as HDAC inhibitors, as well as some novel monoclonal antibodies. In addition, we have trials where we are combining some of these new biological therapies with conventional chemotherapy as a first line treatment for patients with lymphoma. We also have trials for patients undergoing bone marrow transplant. Specifically a novel conditioning regimen to prepare patients for the transplant that involves the use of extracorporeal photopheresis, which is a light based therapy that modulates the immune systems of the patient so that they do not develop graft-versus-host disease.
- Chu This last study is quite important because as you said earlier, one of the big problems with transplantation is the increased risk of developing graft-versus-host disease. What you have found previously is that with this new treatment you can dramatically reduce that side effect and still maintain the good effects against the lymphoma.
- Foss That is right, prior to our doing this study, the only way to deal with graft-versus-host disease was to give drugs to the patient ahead of time as well as after the transplant. This approach involves ultraviolet light treatment to the white blood cells of the patient. It does not involve a drug and is a novel approach to try to condition the patient before the donor T-cells or the stem cells are put into the patient. Using this approach, we have shown that we have reduced the incidences of acute graft-versus-host disease significantly in over 120 patients who received this kind of transplant regimen.
- Miller Who is involved in terms of seeing the patient; who is on that team when the patient comes to Yale or another medical center?
- Foss It is important for patients to know that there is more than just their doctor on their team. Many teams have a nurse and a nurse practitioner as well as clinic nurses that get to know the patient if they come in frequently. We have social workers that work as a part of our team and a nutritionist that comes by and visits every patient while they are waiting to see their physician. We also have support groups that the patient needs to be aware of. There are specific support groups for specific types of cancer as well as overall support groups for patients. We also provide information for patients about foundations and societies that may have additional information. Such as in the case of lymphoma, there is the lymphoma research foundation and there is a leukemia lymphoma society. Both of these organizations do have Connecticut Chapters and are very active with our patients.

- Chu Francine, as we near the end of the program this evening, I want to get your thoughts on how the landscape for the treatment of lymphoma has changed and evolved over the past 20 years since say we were fellows at the NCI.
- Foss About 20 years ago or so, we thought that the only approach to treating lymphoma was to give chemotherapy drugs. Essentially, these were the same kind of chemotherapy drugs we gave for other tumor types. Now that we understand the biology of the lymphomas a little bit better due to basic research, we have been able to identify specific proteins and receptors so that we can develop targeted therapy. We have also been able to understand the mechanism by which these cells grow, and have been able to develop drugs that are much more specific. In addition, we have been able to develop drugs that have very little toxicity for the patient. The major goal now is to get patients into remission and then maintain them. We have also learned that after giving chemotherapy, if we do not do anything, the patient may relapse. We have developed a whole different strategy for patients now that may involve not only our initial therapy, but also some ongoing treatment; in some cases for the rest of their lives.
- Miller Where do you think things are headed if you were to make some predictions for the next 5 years?
- Foss One of the interesting things about some of these new drugs is that they may in fact change the natural history of lymphoma. While we used to say that we could not cure patients with low-grade lymphoma, they may in fact be cured by some of these novel treatment approaches. It is just going to take us another 5 or 10 years to follow these patients to know for sure whether these treatments really are curing them. The future is very bright for lymphoma because there are a lot of new drugs, a lot of new treatment strategies, and overall survival for most patients is getting better if we look over the last 10 years.
- Chu Francine, thanks, it has been great having you. It has been very informative and we look forward to having you on a future program to give us an update as to where things are. Until next week, this is Dr. Ed Chu and Dr. Ken Miller from the Yale Cancer Center wishing you a safe and healthy week.

If you have questions, comments, or would like to subscribe to our podcast, go to www.yalecancercenter.org where you will also find transcripts and past broadcasts in written form. Next week we pay tribute to breast cancer awareness month.