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**Guest Expert:
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Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. 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 week, Dr. Francine welcomes Dr. Iris Isufi. Dr. Isufi is Assistant Professor of Hematology at the Yale School of Medicine. Here is Francine Foss.

Foss Let's start off by having you tell us a little bit about how you came to Yale? You are new on the faculty.

Isufi I completed my training, my residence training, in New York and was interested in the field of hematology very early on, particularly in the areas of lymphoma and bone marrow transplantation. When it came to deciding on a program for my fellowship training, I chose Yale, hence I came here about four years ago and the reasons why I chose Yale to do my fellowship are because there is a very strong lymphoma program here with many referral from many private oncologists and community hospitals with many aggressive cases of lymphomas being treated, both autologous and allogeneic stem cell transplantations were being performed, and I have been here ever since, and this is my fourth year at Yale.

Foss The whole field of bone marrow transplantation is a little bit different than hematology, although it is in hematology. There are not many people that are interested in bone marrow transplant anymore, so can you tell us what it is about bone marrow transplant that particularly interested you?

Isufi Throughout my training I saw people with many different hematologic conditions including lymphomas as well as leukemias, particularly young patient's being diagnosed in their teens or early 20s. Some of these patients responded to the treatment with chemotherapy, but most patients unfortunately relapse and many of them died, and this was very disheartening to see and I was looking for a field that provided some of these patients a chance for cure, and the field of bone marrow transplantation, despite its challenges, is one of the areas that provides hope and the chance for cure to many patients who would otherwise have no chance.

Foss We talk about bone marrow transplant, but we do not actually use bone marrow that often. Can you tell our audience a little bit about the different kinds of transplantation and what sources we get the cells from?

Isufi We used to use bone marrow transplantation pretty commonly in the past and this involved a procedure where the donor of the bone marrow cells would have to go to the operating room and

3:31 into mp3 file http://yalecancercenter.org/podcasts/2011_1030_YCC_Answers_-_Dr_Abhyankar.mp3

receive a general anesthetic and it was at times a painful procedure for them. More recently, however, we have been obtaining the stem cells not from the bone marrow itself, but from the peripheral blood of the donor, and sometimes this could be the patient themselves or an alternate donor. A catheter is placed and they are connected to a machine and these stem cells are collected through the peripheral blood and this is the source that is most commonly used now, except for a few diseases where bone marrow is still preferred.

Foss And are we using umbilical cord blood as well?

Isufi That is correct, umbilical cord blood is also used as a stem cell source.

Foss You mentioned autologous and allogeneic transplant. Can you explain the difference between those two?

Isufi Autologous stem cell transplantation is the procedure whereby the patient serves as a donor for the stem cells. The patients have a hematologic condition that either has relapsed or is very aggressive and they require a transplant and very high doses of chemotherapy, which, unfortunately, while at the same time it is killing the disease, it also affects their bone marrow and their ability to make new blood cells, namely, the white blood cells, the red blood cells, and platelets, by obtaining their stem cells in advance and then subsequently giving them high doses of chemotherapy, we give them a chance to place these cells back into them following chemotherapy and forming new blood cells again.

Foss So, basically you are able to take a patient's own bone marrow cells that are circulating in the blood and put them in the freezer?

Isufi That is correct.

Foss And then use them later on. So patients ask the question, why don't we do this in all patients. I know the issues with respect to which patients are appropriate for that approach, but can you just tell us with autologous transplant, what is the ideal patient and when would it not be appropriate?

Isufi I think an ideal patient to undergo an autologous stem cell transplant would be a patient who has, for example, a very high-risk lymphoma that has relapsed. These patients, while they may respond to chemotherapy again, they have a very low chance to stay in remission and by giving them high dose chemotherapy and a stem cell rescue at the end, we provide most of them with the chance for cure, and if not cure, a very prolonged remission. However, not everyone qualifies for high-dose

6:49 into mp3 file [http://valecancercenter.org/podcasts/2011_1030_YCC_Answers - Dr_Abhyankar.mp3](http://valecancercenter.org/podcasts/2011_1030_YCC_Answers_-_Dr_Abhyankar.mp3)

chemotherapy and autologous stem cell transplant, other factors have to be taken into consideration such as other comorbid illnesses that they might have and their organ functions such as the heart and the lungs and their ability to withstand such a procedure.

Foss What if a patient say is not in remission after they have had chemotherapy, would you be able to do a transplant in that setting?

Isufi I think if an autologous stem cell transplant is done in that setting the patients would be at a significant risk for relapse. Hence, the best patients to receive an autologous stem cell transplant would be the patients that go into remission with a second line chemotherapy or a combination of chemotherapy and immunotherapy or other agents that put them into remission before the transplant, and for some of these patients who cannot be put into remission with chemotherapy and who still have some disease, we would consider performing an allogeneic stem cell transplant and for this type of transplant the source of the stem cells is either a patient's sibling or sometimes if a sibling is not a match, we have to look for an unrelated donor or for cord blood as a stem cell source. And the way we do that is that we look at certain genes and proteins that both the patient's, the recipients and their donors have and try to match those.

Foss At this point in time, is there an age limit for transplantation?

Isufi We no longer consider chronological age. We use more of a biological age when we consider transplant, and while in the past the only transplants performed used very high doses of chemotherapy and radiation, called myeloablative stem cell transplants, more recently, reduced intensity transplants have also been used where we rely less on the high doses of chemotherapy and more on the immune system of the donor to fight either the leukemia or the lymphoma and this type of transplant can also be performed in patients at more advanced age, or sometimes with other problems with organ function.

Foss You talked about the reduced intensity transplant regimens that are a lot easier to take than in the old days when we had very toxic therapy. Do most patients do well with those conditioning regimens, do patients get sick, and what is chance that you run into trouble if you have a reduced intensity transplant compared to the way we used to do it with the ablative transplant?

Isufi Patients actually tolerate these regimens much better, particularly elderly patients who may have preexisting dysfunction in their heart, lungs, or problems with diabetes and they are overall better tolerated, although some of the complications that result from an allogeneic stem cell transplant, even with reduced intensity conditioning, are similar to the complications that we see with myeloablative or with very high dose chemotherapy, particularly with graft-versus-host disease,

**10:31 into mp3 file [http://yalecancercenter.org/podcasts/2011_1030_YCC_Answers -
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which is one of the more common complications that people get following a transplant and is also common following reduced intensity conditioning.

Foss Can you define graft-versus-host disease? What is it and does it only happen after the allogeneic transplant?

Isufi This is a syndrome where the donor's immune system actually recognizes the recipient, or the patient that were treating with a hematologic condition, as foreign and it tries to attack it and this is a normal function of an immune system. It is what an immune system should do, however, it is not the intended result in this scenario and there are two types of graft-versus-host disease that we recognize, one being acute graft-versus-host disease which commonly occurs in the first few weeks and even months following transplantation and this particularly affects the skin, the liver, and sometimes the gut of the patients, resulting in diarrhea, and then there is a chronic form of graft-versus-host disease, which can really develop at anytime and it affects a different set of organs, patients can get dry eyes, dry mouth, they can have liver abnormalities, sometimes they can have thickening of the skin and sometimes problems with their joints. We administer immunosuppressive medications to minimize the risk of this happening and when it does occur and it is more severe, we have several different drugs to treat it. Primarily, we treat it with steroids.

Foss Can you give us an idea of how often patients develop bad graft-versus-host disease?

Isufi Graft-versus-host disease is quite common and it ranges in the literature depending on the type of the chemotherapy that is used before transplant and can vary anywhere between 20% to 60% in certain patient subgroups, the risk is less if cord blood is used as a stem cell source. The risk of severe graft-versus-host disease, however, is much less, probably in the order of 20% or so.

Foss In some cases it can actually be very severe?

Isufi Yes, in some cases it can be quite severe and even fatal, unfortunately.

Foss But on the flip side there are a lot of patients that get better as well.

Isufi Yes, on the flip side there are many patients that get cured and it is always a difficult decision for both the patient and the treating physician to make sure that those risks and benefits are placed on balance in order to find the right timing for performing such a transplant.

Foss We are going to take short break for a medical minute. Please stay tuned to learn more information about bone marrow transplantation with Dr. Iris Isufi.

**13:56 into mp3 file [http://yalecancercenter.org/podcasts/2011_1030_YCC_Answers -
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*Medical
Minute*

It is estimated that nearly 200,000 men in the US will be diagnosed with prostate cancer this year, and one in six American men will develop prostate cancer in the course of his lifetime. Fortunately, major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from this disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical exam, and a blood test. With screening, early detection, and a healthy lifestyle, prostate cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers, like the one at Yale, to test innovative new treatments for prostate cancer. The da Vinci Robotic Surgical System is an option available for patients at Yale that uses three-dimensional imaging to enable the surgeon to perform a prostatectomy without the need for a large incision. This has been a medical minute and more information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Foss This is Dr. Francine Foss and I am joined today by my guest Dr. Iris Isufi. We are discussing bone marrow transplant and hematologic malignancies. In the beginning of the show Iris, we talked a lot about bone marrow transplant. I would like to start this half of the show off by talking a little about some of the other hematologic malignancies. I understand that you are very interested in lymphoma as well. Can you tell us a little bit about lymphoma? What are the different types of lymphoma and what are the treatment options for patients with lymphoma?

Isufi Lymphoma is quite common, according to this year's database which is published by the National Cancer Institute, just in 2011, about 75,000 patients, both men and women, were diagnosed with lymphoma and the median age of diagnosis is about 64 years, although this can occur in patients less than 20 years old and also in patients who are more than 85 years old and the incidence is estimated to be about 23 in 100,000 men and women per year. Lymphomas arise from abnormalities in cells of the immune system. There are several types of cells in the immune system. The two main subtypes are the B and T cells and lymphomas can arise from both of these cell subtypes, and I am specifically interested in the B-cell lymphomas and this is a very wide range of diseases that have many commonalities, but also many differences. Some of these lymphomas follow a more indolent or slow growing course, while others tend to behave very aggressively.

Foss Can you tell us what the risk factors are for developing lymphoma?

**16:55 into mp3 file [http://yalecancercenter.org/podcasts/2011_1030_YCC_Answers -
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- Isufi We know many things, which are not risk factors for the development of lymphoma, for example, there has not been an association with smoking, alcohol, obesity, or diet modification contributing to lymphoma. There has been, however, a link between certain exposures during one's lifetime with non-Hodgkin lymphomas such as exposure to older hair dyes or to certain agricultural pesticides and insecticides. There is also a relation between compromised immune function and lymphoma and this is seen with certain autoimmune conditions. For example, systemic lupus erythematosus or autoimmune thyroiditis or Sjogren's disease, have an increased incidence of lymphoma and also patients with the human immunodeficiency virus, HIV, and also some patients from the Caribbean basin with another similar virus called HTLV1 are at increased risk for development of lymphoma. There is a host of other viruses such as the Epstein-Barr virus, hepatitis-C, human herpes virus 8, also known as the Kaposi sarcoma virus, which have been associated with certain subtypes of lymphoma.
- Foss You talked about two different types of lymphoma, the indolent and the aggressive. Can you talk a little about how they present clinically and how they are treated?
- Isufi The most common presentation for these types of lymphomas is with adenopathy, which is enlargement of the lymph nodes. This can be seen in the neck, in the armpits, or sometimes the groin, and these are oftentimes felt by the patients and sometimes by a physician during a routine exam. These lymph nodes can also be found in other areas of the body such as in the chest or abdomen and are not felt by the patient or the physician, but can only be detected in scans. The enlargement of the lymph nodes is often painless, particularly in the case of the indolent or slow growing lymphomas with more aggressive lymphomas because of the rapid growth from the lymph nodes and sometimes stretching of the capsule. The patient can feel uncomfortable or even have pain. In addition to the swollen lymph nodes, the patients can also experience other symptoms such as low grade fevers, night sweats, decreased appetite, and weight loss, so called B-symptoms.
- Foss And are there differences in terms of how you treat these diseases?
- Isufi We treat these diseases quite differently, for example, for the low grade or the indolent lymphomas, treatment can vary from the watch and wait approach, where we monitor these patients carefully without introducing any treatment, to treatment with monoclonal antibodies alone, to treatment with a combination of chemotherapy and antibodies, for the more aggressive lymphomas, we treat upfront usually with a combination of chemotherapy that also includes a monoclonal antibody.

20:56 into mp3 file [http://yalecancercenter.org/podcasts/2011_1030_YCC_Answers -
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- Foss We talked about the bone marrow transplant as a treatment modality for some of these patients, mostly after relapse, can you talk about how you use bone marrow transplant as you are treating and following a lymphoma patient over time, at what point is it appropriate to think about a bone marrow transplant?
- Isufi Most of the patients with aggressive lymphomas we treat upfront with chemotherapy alone. However, if/when their disease comes back, if it is indeed again sensitive to chemotherapy now is the time to perform a bone marrow transplant and in this setting we would normally perform an autologous stem cell transplant where we would give very high-dose chemotherapy and use the patients own stem cells to reconstitute all of their blood cell types in the end and oftentimes this type of transplant will put at least 50% of these patients into remission, whereas without the transplant they would have a much lower chance of longstanding remission or cure. For the indolent lymphomas, oftentimes we go through a series of treatment with either monoclonal antibodies or different chemotherapy agents, sometimes single agents sometimes combined, before we consider performing a stem cell transplant. In this group of patients, we also use radioimmunotherapy, which is a combination of these monoclonal antibodies and radiation to target specifically these lymphoma cells both with a monoclonal antibody that is bound to a radioactive agent and this can be performed either alone or in combination with a stem cell transplant. This sub group of patients tends to respond well not only with an autologous stem cell transplant but also with an allogeneic stem cell transplant, which is performed with cells from a donor and in that setting the patient can go into transplant with some disease. They do not have to be in complete remission prior to transplant. Of course it is better for them to go into transplant with the lowest amount of disease possible, but we rely on the immune system of the donor to fight any residual lymphoma in that case.
- Foss Iris, it sounds like the management of most lymphoma patients is really complicated and involves a multidisciplinary approach. Can you talk about that multidisciplinary team at Smilow Cancer Hospital and how we integrate with each other to treat these patients?
- Isufi The multidisciplinary team at Smilow Cancer Hospital meets several times a week, at least twice a week, and during one of these meetings we will discuss a patient with lymphoma, and during another meeting we discuss a patient with another hematologic condition such as leukemia, myelodysplastic syndrome, myelofibrosis, or aplastic anemia, which are diseases where a transplant is a consideration. During these meetings, transplant team members, and also radiation oncologists, pathologists, and radiologists are present to discuss all cases to come up with the best treatment plan and individualized plan for each patient.

25:06 into mp3 file [http://yalecancercenter.org/podcasts/2011_1030_YCC_Answers -
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- Foss So most of these patients have a consensus opinion about their treatment prior to them actually getting treated?
- Isufi That is correct, and this is done not only for new patients who come to Yale, but also for patients with difficult diseases, where the treating physician has management questions at any point during the disease course.
- Foss And the unit at Yale is unique in another way, and that is that it is an integrated unit, where the same physicians who are treating primarily the lymphomas but also the leukemias to some degree also are the bone marrow transplant physicians who follow the patient right through their transplant. Can you talk a little bit about the continuity of that care?
- Isufi The continuity of care is one of the great things about Yale because, as you said, we often treat our patients with lymphoma up until the point where they need to transplant and we have known these patients at times for a number of years before we take them into transplant and they are known not only by the physicians, but also by both the inpatient and outpatient nursing staff and it provides a very familiar environment for them to come to, particularly as they are going through this difficult treatment. The other great thing about Yale that not many institutions have that is very relevant and important to transplant is the Day Hospital that we have for transplant patients, where they have one-on-one individualized nursing care in an environment with minimum risk of exposures to infections.
- Foss Also on the other side, we have a lot of patients, we do not talk much about this, but a lot of patients who are cured with lymphoma and even after bone marrow transplant. Do those patients still come back to see us and how often? What are some of the issues that we deal with in that setting?
- Isufi We try to follow our transplant patients long term because there are long term consequences following transplant and even for our patients who are considered cured of their disease and are several years out from transplant and off all of the immunosuppressive medications, we follow them at least once a year because they do develop secondary malignancies such as cancers of the skin and cancers of other solid organs as well as other problems particularly related to their endocrine functions such as problems with their thyroid gland and other hormones.
- Foss What about the lymphoma patients that are cured? How often do you see those patients and what kinds of issues could they run into?

28:23 into mp3 file [http://yalecancercenter.org/podcasts/2011_1030_YCC_Answers -
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Isufi Lymphoma patients who have undergone transplant, we also tend to follow over a long period of time because even though they are cured from their primary malignancy, a subset of these patients are at risk for the development of other malignancies and at times even other types of lymphomas. So, we do follow them several years out from transplant.

Dr. Iris Isufi is Assistant Professor of Hematology at Yale School of Medicine. If you have questions or would like to share your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.