

Yale CANCER
CENTER

answers

WNPR Connecticut Public Radio



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A Review of Hematological
Malignancies

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. 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 1-888-234-4YCC. This week, Francine Foss welcomes Dr. Nikolai Podoltsev. Dr. Podoltsev is Assistant Professor of Hematology at Yale School of Medicine and he joins us this week for a conversation about hematologic diseases. Here is Francine Foss.

- Foss Can you start off by telling our listeners a little bit about hematologic diseases? What does hematology mean?
- Podoltsev Hematology is a science about blood and blood disorders and there are a number of diseases which we divide into malignant and benign in hematology. The benign hematological conditions are related to different blood cells we have, and include problems with red blood cells and usually we are talking about anemias, and also problems with platelets. We have platelets to protect us against bleeding. So, you can have problems related to platelet function and their number. Sometimes, you have a decreased number, sometimes you may have an increased number, and also there are white cells, and white cells are important to fight infection. When we have low white cells, this may be associated with the risk of infection; this is benign. The malignant group involves things that people usually hear about, including leukemias and lymphomas.
- Foss I think the important point for our listeners is that if you do go to see Dr. Nikolai, you do not necessarily have a cancer.
- Podoltsev That is correct. More than half of my patients at this point have benign conditions.
- Foss Can you tell us a little bit about the hematology program at Yale?
- Podoltsev The hematology program at Yale involves inpatient and outpatient care for patients with hematology problems. Our inpatient care includes three services. Service number 1 is the service for acute leukemia and lymphoma patients who are admitted to receive intense chemotherapy treatment in the hospital. The next service is the service for patients who are coming in for allogeneic stem cell transplantation as part of management for their malignant hematological conditions. And finally, we have a hematology consultation service. This service provides consultations to different departments in the hospital and is available 24x7.
- Foss Can you explain how the specialty of hematology fits in with oncology? Is it a separate specialty? Are there doctors that just practice hematology and not oncology?
- Podoltsev If you go to a private hematologist-oncologist, usually, this physician will be providing care for both hematological and oncological diseases. In university centers in big academic institutions, we

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have an opportunity to have a group of people who are working only with hematological conditions, and I think this may give a certain depth at times when you come for the management of conditions, which may be quite complicated. That is why at Yale Cancer Center we have a separate group of physicians who are doing hematology only.

Foss And they are doing both the inpatient and the outpatient?

Podoltsev That is correct. We do have hematologists who are mostly focusing on an outpatient and hematological consultation service and we do have hematologists who subspecialize and work mostly with malignant hematology diseases including leukemias and lymphomas.

Foss Can you tell us a little bit about what got you interested in hematology?

Podoltsev I am from Russia originally and both of my parents are physicians, and my mother happens to be a hematologist who is still actively practicing in St. Petersburg, Russia. So, I think I got interested in this in childhood and when it came time to make decisions about specialization in medical school, I did not really have any other thoughts. And that is how I got involved with hematology.

Foss A mother's influence then?

Podoltsev That is correct!

Foss In Russia, of course, there was the Chernobyl incident and there were a lot of issues related to that associated with hematologic malignancies and leukemias. Did that influence you in any way?

Podoltsev That happened in 1986 and at the time I was finishing high school. I would not say this influenced my decision because by that time I was already considering medicine as my career and I was thinking about hematology. We did not really see too many patients from that area in St. Petersburg, because we are quite to the north of this region.

Foss You mentioned leukemia as one of the hematologic malignancies we commonly think about. Could you just go through for our listeners what the different kinds of hematologic malignancies are; what are the most common ones and the different types?

Podoltsev I was looking into that because and actually found some statistics, and the most common hematological malignancy is actually non-Hodgkin lymphoma. In the United States, we diagnose approximately 65,000 cases a year, which makes it the number 5 disease in men and number 6 in women, if you take all of the cancers. The second most common would probably be AML, acute myelogenous leukemia, with 12,000 cases, followed by CLL, which is chronic lymphocytic leukemia, with 10,000 cases. The other conditions which we see less frequently include acute lymphoblastic leukemia and chronic myelogenous leukemia. This is pretty much the group of malignant conditions we deal with in malignant hematology.

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Foss And we know that some of these diseases increase in frequency as you get older?

Podoltsev Pretty much all of them do. Most of our patients are older with an average age probably somewhere between 60 and 70.

Foss Of course, leukemias also occur in children?

Podoltsev That is right. There are types of acute leukemia which are more frequent in children. These are acute lymphoblastic leukemia, and I personally do not treat children, but the results of treatment have improved dramatically over the years and currently most of these patients are cured. Unfortunately, the same type of leukemia, when seen in adults, we cannot really say that we are as successful with managing it. Only 30% of adults who are diagnosed with acute lymphoblastic leukemia will survive 5 years, and the equivalent number for children is above 80%.

Foss It is interesting when you talked about the number of acute myelogenous leukemias and it was actually higher than the number of chronic lymphocytic leukemia patients?

Podoltsev That is correct!

Foss But we seem to see a lot more CLL patients in the clinic. Is that just because they have the disease for such a long period of time?

Podoltsev Yes, I think the difference here is acute and chronic. Acute leukemias, unfortunately, are a lot more dangerous and a lot more patients die from that disease, while chronic lymphocytic leukemia is chronic and that is why a lot of people live with this disease for many years.

Foss That word ‘chronic’ is a word that really was coined in the setting of leukemias and lymphomas where we start talking about these chronic diseases, it is not as common in the solid tumor area, but, we have got chronic low-grade lymphomas and we have got these chronic leukemias. How do you talk to a patient about that when you talk about a disease that they are going to have for a long time?

Podoltsev Interestingly, acute disease is usually easier to cure, but when we do not cure it, that disease may kill you. With chronic disease, the chances for cure are less, much less, but you live a lot longer with it, a lot of times even without treatment. That is what I am talking to the patients about. When they have a chronic hematological malignancy, they may live with this condition for a long time, especially now when we have more and more new drugs available to keep them alive and without symptoms related to their chronic condition.

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- Foss Do you find it difficult getting patients to accept the fact that they may not actually need a treatment for their disease?
- Podoltsev I think a lot of people are actually happy when I say that, and I was working in internal medicine for a while and I always thought that to say to someone that he does not need a pill takes a lot of knowledge. I think similar situations are present in malignant hematology when you are dealing with chronic leukemias. Here you have to be very assuring. You have to be able to explain to the patient in plain language what his or her disease means and why we do not have to treat it right away.
- Foss One of the easy things about taking care of leukemia is that you can take some blood out and look under the microscope, so you have a fairly good indication of what is going on with their disease.
- Podoltsev I think this is another thing which I have to mention, when you were asking me about why I got so excited about hematology and why I started to do it, it's partly because I was always excited that I can see those cells under the microscope and sort of track visually what is going on. We routinely go to the lab to look at the peripheral smear when patients are coming to us for initial consultation, not only with malignant hematological diseases, but also with benign diseases, and it gives us a lot of good clues about further workup and their diagnosis.
- Foss That brings up a very good point, Nikolai, and that is that as a hematologist you do not function in isolation, you really depend on a lot of different areas of the hospital such as the blood bank and many other services to come together for the management of your patients.
- Podoltsev Yes, we apply a multidisciplinary approach. This approach is always emphasized in the field of oncology, but we also use it to the benefit of our patients. I do interact routinely with our pathologists because I cannot really say what type of diagnosis my patients have without their consultation. A lot of times I have to interact with our lab medicine physicians about test results when I need to order certain tests. To give the explanation to the patient, I first talk to the laboratory physicians to get a clear idea of the meaning of this multiple and sometimes very complicated test. We also interact with radiologists because a lot of our patients get different types of imaging. We talk to other different subspecialists including physicians in the blood bank as many of our patients have to receive different blood products relatively frequently.
- Foss Can you talk a little bit about this whole condition of myelodysplastic syndrome? This is also something that a hematologist takes care of. It is a little bit unclear, I am sure to our listeners, what we are talking about when we say myelodysplastic syndrome.
- Podoltsev It may be a bit confusing because there is another group, which is called myeloproliferative diseases and we also take care of those patients as well. Both of these groups are under the umbrella of chronic myeloid disorders. As you notice, they are chronic, and that means that the patients with these conditions may live for quite some time and sometimes do not need treatment.

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Myelodysplasia is the condition which affects the bone marrow stem cell, and bone marrow is the factory of all blood cells and stem cell is what gives us red blood cells, white cells, and platelets. If there is disease which affects that stem cell, we may have problems and we develop so-called cytopenias. Basically, your counts for red blood cells, white cells and platelets decrease and you may suffer from its consequences including anemia, thrombocytopenia when the platelet count is low, as well as neutropenia when your white cell count is low. Thrombocytopenia predisposes you to bleeding and neutropenia to infection. Usually, when you look in the bone marrow, and we do that by performing bone marrow biopsies, we can find the problem and establish the diagnosis. Interestingly, bone marrow is actually not empty. There are many cells there, but at the same time in the blood, we see the deficiencies. We see low counts for red blood cells, platelets, and white cells. That is the characteristic feature for most of the patients with myelodysplasia.

Foss Just to touch on what you mentioned about the bone marrow biopsy for our listeners, do they need to worry about getting a bone marrow biopsy? Is this is a painful procedure and what do you actually do?

Podoltsev This is one of those procedures I do routinely, pretty much every week, and I think it is quite benign. Of course, there is certain discomfort, which we try to negate by administering intravenous as well as local medication. I do not think our patients have to worry about that. Not every one has to have the bone marrow biopsy, but this is something we definitely discuss frequently with our patients.

Foss We would like to talk a little bit more about some of these hematologic disorders when we come back from our short break for a medical minute. Please stay tuned to learn more information about hematologic diseases from Dr. Nikolai Podoltsev.

*Medical
Minute*

This year, over 200,000 Americans will be diagnosed with lung cancer, and in Connecticut alone there will be over 2,000 new cases. More than 85% of lung cancer diagnoses are related to smoking, and quitting even after decades of use can significantly reduce your risk of developing lung cancer. Each day, patients with lung cancer are surviving, thanks to increased access to advanced therapies and specialized care. New treatment options and surgical techniques are giving lung cancer survivors more hope than they have ever had before. Clinical trials are currently under way at federally designated comprehensive cancer centers, like the one at Yale, to test innovative new treatments for lung cancer. An option for lung cancer patients in need of surgery at Yale Cancer Center is a video-assisted thoracoscopic surgery, also known as a VATS procedure, which is a minimally invasive technique. This has been a medical minute. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined today

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by Dr. Nikolai Podoltsev to discuss the issue of hematology, both benign and malignant conditions. Nikolai, before the break we were talking about the myelodysplastic syndrome, which you said is characterized by not many cells being produced by the bone marrow stem cells. You also mentioned myeloproliferative disorders. Can you compare and contrast those two for us?

Podoltsev As I said, they both belong to chronic myeloid disorders. Myelodysplasia affects the stem cell and we do have cells in the bone marrow, but unfortunately we do not have normal cells in the circulation in most of these patients, and that is why they suffer from anemia, which requires transfusions, sometimes thrombocytopenia and neutropenia. Now, myeloproliferative diseases also are due to problems in the stem cell, but these patients will have normally functioning cells, but a lot of times they will have more than necessary and those cells will cause problems, not anemia, but erythrocytosis for the condition called polycythemia vera; not thrombocytopenia but thrombocytosis for a condition called essential thrombocythemia. We do have problems which are slightly different to myelodysplasia we have to deal with, and this includes increased incidences of stroke, for example. The conditions are similar in a way because myelodysplasia, as well as myeloproliferative diseases, may evolve in acute leukemia. Usually, it is acute myeloid leukemia.

Foss How do these patients usually present to you?

Podoltsev Patients with myelodysplasia usually come to us with symptoms related to one of their cytopenias. More frequently, it is anemia and manifestations of anemia including fatigue or shortness of breath, for example. Sometimes it is bleeding because their platelets may be low. Sometimes, they also may have infections, but it is less frequent. Patients with myeloproliferative disease, they may present just because their primary physicians ordered a blood test, which showed an increased number of red cells or platelets, and sometimes they will have itching, especially after a hot shower or they have this manifestation called erythromelalgia, they have burning pain of their hands and feet, and skin redness sometimes associated with swelling. Those are not very frequent, but if present, make us think about one of the myeloproliferative diseases.

Foss How often does somebody need to worry about a myeloproliferative disease if say they go the doctor and their white count is a little bit elevated, do they need to worry?

Podoltsev I see a lot of these patients because apparently their primary care physicians are worried about that, but most of the time there are other reasons why the white count is mildly elevated, and one of those reasons is smoking, which is frequently associated with a slight elevation of the white count. I have to counsel those patients about smoking cessation, stressing that they have these manifestations, but also there are a lot of other harms that smoking may be associated with.

Foss Are there also medications that can cause either the blood counts to go up or the blood counts to go down?

Podoltsev Yes, this is not too frequent but some patients are taking prednisone or other steroids which may

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cause elevation. Some patients with psychiatric conditions may be on lithium, which may cause elevation of the white cells as well.

Foss You mentioned that the myeloproliferative disorders oftentimes can lead to leukemia. Could you elaborate a little bit on that for us?

Podoltsev I would say that myelodysplasia is more frequently an issue when you are thinking about acute leukemia because the other term we use for myelodysplastic syndrome is preleukemia. The rate of progression is different depending on the prognostic factors, which we can look at, at the beginning. Speaking about myeloproliferative diseases, the incidence of acute leukemia in these patients is less, so if you compare them to myelodysplastic patients, and depending on the condition, it varies between 5% and 20% overall. So, do you have to worry about it? It really depends on what type of myeloproliferative disease you have.

Foss Recently, there have been some new discoveries in myeloproliferative syndromes in terms of some genes, for instance, that are aberrant that we could use as markers for these diseases. Do you want to talk about that?

Podoltsev I did not really mention chronic myelogenous leukemia yet. This is a special type of myeloproliferative disease for which we have a special treatment. This is a targeted therapy and there are a few drugs now, but it all started with imatinib, which at the beginning of the century was probably the first drug in this targeted therapy group, and has expanded to a lot of other conditions. It targets the product of the translocation called Philadelphia chromosome, and this product is actually responsible for making cells malignant in the case of chronic myelogenous leukemia. So, if we can inhibit its action, we can reverse that malignant process. Imatinib is the drug which does that, and it does it specifically for this Philadelphia chromosome product. What happens is you do not cure the disease, but you make it more chronic. People can live with this disease a lot longer without worrying about its progression.

Foss What happens if a patient who is on imatinib for a period of time develops a resistance say to that drug?

Podoltsev We have two other drugs at this point approved by the FDA, which we may use if patients develop resistance. Unfortunately, some of the patients develop a certain type of resistance for which we do not have a drug yet. Studies are ongoing trying to identify a medication that may be useful in these circumstances.

Foss Prior to having these drugs, if you had say CML, you would be treated probably with chemotherapy and a bone marrow transplant?

Podoltsev Yes, and even now, basically the only cure for CML we know for sure is allogeneic stem cell transplantation. In fact, this is true for most of our hematological malignancies. This is the cure,

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and that is why we still do these types of treatments for patients even in the era of imatinib and other targeted therapies.

Foss In this era of personalized medicine, are we routinely looking for these specific mutations in all of our patients with leukemia?

Podoltsev We do look for certain chromosomal abnormalities for which we have targeted treatment and the Philadelphia chromosome may be identified not just in patients with CML or chronic myelogenous leukemia, but we also see this reasonably frequently in older patients with acute lymphoblastic leukemia, and if we identify it in those patients, now we can use imatinib or other medications from the group to take care of those patients and again, we are probably not curing them, but we help them to live longer.

Foss In terms of other progress that you see in hematology, obviously imatinib was a huge step forward for us, but are there other new drugs or new therapies that are being developed for these diseases?

Podoltsev I think it is not about the new drugs, but I just want to start with supportive care, which became much better, and that is why our patients are able to tolerate toxic treatments much better with less side effects. Some of those side effects in the past were killing the patients, including infections, and now we have very good antibiotics. We also have great blood products. We have G-CSF erythropoietin to support these patients through the treatment. There are also new medications, which we are using in different hematological malignancies including hypomethylating agents for myelodysplasia, and that is why I think these patients are now living longer and we see more and more of them surviving, and that is why this field becomes more and more attractive. There are some other medications which became available to us in the management of non-Hodgkin lymphoma, for example. Rituximab is the monoclonal antibody which targets certain antigens on the surface of the lymphoma cells, and introduction of this drug into treatment of these patients improved their survival significantly. There is progress being made in different directions and in different diseases in malignant hematology.

Foss In the last couple of years, there have actually been two drugs approved for CLL, bendamustine and alemtuzumab.

Podoltsev Bendamustine is more on the side of classic chemotherapy agents and this is the drug which was available in Europe for a long time and now was moved to the United States market and has great success in patients with indolent lymphomas including CLL. Alemtuzumab is a new generation anti-CD20 antibody, which we now can use for CLL. We will see if it gets the indication for other lymphomas as it looks pretty attractive, especially for patients who, for example, cannot tolerate rituximab.

Foss What are the side effects of these new therapies, say alemtuzumab?

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Podoltsev Whenever you use the antibody, you always think about allergic reactions, and I think infusion reactions are the main problem with both alemtuzumab and rituximab, and that is why it takes a long time to administer them. We do take precautions when we give these medications, and it is known that if you take more time to give it, there is less likely a chance that you will develop the reaction.

Foss In other words, tell the patient to bring multiple books to the clinic.

Podoltsev That is right, especially for the first time you receive them, it will be a long day.

Foss You mentioned the hypomethylating agents, and I was interested in that because, again, that is another whole new class of drugs that works by a completely different mechanism. Can you talk a little bit about that?

Podoltsev Hypomethylating agents and histone deacetylase inhibitors are two classes of drugs which were recently introduced in the malignant hematology world, and they are epigenetic drugs. They do not influence the gene directly, but indirectly, and whatever silenced is now not silencing the gene, and that is why the cell may function more normally and die as is necessary for cells.

Foss They really convert the cells more toward a normal type.

Podoltsev That is right. We are reversing, we are trying to reverse their malignant nature and make them more normal.

Foss Those are treatments that are given over a long period time?

Podoltsev That is correct. I can say for hypomethylating agents, for example, first of all, it takes some time for them to really work. We have to give them for a few months before we can say that they did work or they did not work, and then we basically continue until we see that they are not working anymore.

Foss When you think about these leukemias that you are treating, many of these patients will be on therapy for a long time, but some of them will go on to get a bone marrow transplant at the end.

Podoltsev As I said before, for most of hematological malignancies, allogeneic stem cell transplantation is the way to cure. Unfortunately, this is not an easy treatment with a lot of side effects and we have to be careful when we select our patients for this type of intervention, and the new medications give us an opportunity to reduce the number of malignant cells and prepare those patients for this potentially curative treatment.

Foss To give them treatment that does not involve a lot of chemotherapy, as you mentioned, the side effects of these new medications are a lot different.

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Podoltsev That is correct.

Foss I wanted to focus on the issue of the stem cell. You talk a lot about the bone marrow stem cells with respect to myelodysplasia and myeloproliferative disorders. Can you tell our listeners what are these stem cells and where are they located? How do we use these stem cells in the clinic, because I know we have stem cell therapies now?

Podoltsev The stem cell issue is a little confusing because of a lot of politics involved. When we are talking about stem cells in relation to hematology, we are talking about stem cells which are located in the bone marrow and small numbers of those cells also circulate in peripheral blood. These are the cells which give origin to myeloid and lymphoid lineages and myeloid lineages are responsible for red blood cells, platelets and certain type of white cells, neutrophils. Lymphoid lineages are responsible for lymphocytes, which is another type of white cell protecting you against infections. Now, these stem cells may be collected from the patient or the donor and then used as a part of the treatment when we can give high-dose chemotherapy and wipe out the disease, but unfortunately, it will also wipe out a patient's own marrow stem cells. Then to rescue the patient out of this situation, we have to re-infuse either his stem cells, then that is called autologous stem cell transplantation, or a donor's stem cells, where it is called allogeneic stem cell transplantation.

Dr. Nikolai Podoltsev 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 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.