WNPR CT Public Radio Voice: Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Yale Cancer Answers features conversations with oncologists and specialists who are at the forefront of the battle to fight cancer. Here's Dr. Winer.

Dr. Winer: Welcome to Yale Cancer Answers. I'm Dr. Eric Winer, a medical oncologist and director of Yale Cancer Center. September is Leukemia Awareness Month, so tonight, we're going to be talking about this complex group of blood cancers. We'll discuss the challenges of early detection and also the exciting advances in treatment. Joining us tonight is Dr. Nikolai Podoltsev, a hematologist who specializes in the diagnosis and treatment of blood cancers, particularly leukemia, but also other related disorders. Dr. Podoltsev, thank you for being with us here on Yale Cancer Answers.

Dr. Podoltsev: Thank you for having me, Eric.

Dr. Winer: We haven't spent a lot of time talking about blood cancers, particularly leukemia, on this program, and I'm looking forward to our discussion. As people may have already noticed, you have a bit of an accent, and I think you have a fascinating personal story. You weren't, of course, born in the United States. You were born in a place that many people have emigrated from over the last 20 or 30 years—and even before that. Can you tell us a little bit about your background?

Dr. Podoltsev: Sure. I was born and raised in the Soviet Union, in a city called Leningrad. Neither the country nor the city exists under those names anymore. Now, it's St. Petersburg in the Russian Federation. I came to the United States in 1997 after I finished medical school and some residency training, including hematology training, in Russia. When I arrived here, I had to start over. I began with residency training again, but I didn't have to repeat medical school, fortunately. You might wonder why I chose hematology, and that story actually begins back in Russia. I grew up in a family of two physicians, and my mother was a hematologist. When it came time for me to go to medical school—because there was no other path for the son of two physicians in the Soviet Union—I decided to explore hematology more deeply. I found the field intellectually challenging. My peers often asked me questions about hematology, which motivated me to learn more. I discovered it's a very broad field, encompassing both malignant hematology, like leukemia, and classical or benign hematology. Initially, I learned both sides of hematology and enjoyed helping patients and answering questions for others. That intellectual curiosity led to the development of my skills, which I was able to enhance further when I arrived in the United States.

Dr. Winer: That's such an interesting background. I've personally had an interest in Russian history and Russian language—I even studied it as an undergraduate. Sadly, I've lost most of my ability to speak Russian, but I still find it fascinating. Let's shift gears and talk about the disorders you treat. While we'll spend most of our time tonight talking about acute leukemia, that's not the only disorder you manage. Increasingly, we think of your field as focus-

ing on myeloid malignancies. Myeloid malignancies include acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and what else?

Dr. Podoltsev: When I introduce myself, I tell people that I treat acute leukemias and myeloid malignancies. As you mentioned, myeloid malignancies include acute myeloid leukemia, but they also encompass myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPNs), and other related conditions. The bulk of my patients don't actually have acute myeloid leukemia. Many have other types of myeloid malignancies. There are also some niche conditions that aren't widely known, such as systemic mastocytosis and clonal eosinophilias, which I also treat. In addition to myeloid malignancies, I care for adults with acute lymphoblastic leukemia (ALL). While ALL is technically a lymphoid malignancy, it shares some features with AML. Like AML, it requires specialized skills and urgent care immediately after diagnosis.

Dr. Winer: But to be clear, acute lymphoblastic leukemia is rare in adults, correct?

Dr. Podoltsev: Yes, that's correct. About 6,000 people are diagnosed with ALL annually in the United States, but only about 2,000 of those cases occur in adults. Children with ALL generally have much better outcomes compared to adults. That said, we've made significant progress in treating ALL in adults over the last decade. Several new drugs, particularly immunotherapies, have been approved, which have improved outcomes. However, there's still a lot of work to be done to make further progress.

Dr. Winer: For our listeners, I want to clarify something. While I mentioned that ALL is more common in children than adults, it's still a rare disease overall. Among childhood cancers, though, ALL is the most common type. Thankfully, it's a disease where we've seen great success in treatment, especially in children. Let's move on to acute leukemia in adults, specifically acute myelogenous leukemia (AML). Can you tell us how AML usually presents? I mentioned earlier that early detection is a challenge. My understanding is that there really isn't such a thing as "early detection" when it comes to AML.

Dr. Podoltsev: That's absolutely correct. AML is diagnosed in about 20,000 adults per year in the United States, which still makes it a rare disease. Most patients present with symptoms of bone marrow failure, as the bone marrow—a vital organ that produces all blood cells—becomes overwhelmed by leukemia cells. In AML, leukemia cells replace normal blood-forming cells in the bone marrow, leading to low levels of red blood cells, platelets, and white blood cells. This can result in: Anemia (causing fatigue and shortness of breath), Low platelets (leading to easy bruising or bleeding), and Low white blood cell counts (increasing the risk of infections). Patients can also experience symptoms from leukemia cells infiltrating other organs, though this is less common. For example, bone pain can occur if the leukemia cells infiltrate the bone marrow extensively, or other organs can be affected, causing pain or organ dysfunction.

Dr. Winer: And acute really means acute. When patients present with AML,

they're often very sick and require immediate medical attention, right?

Dr. Podoltsev: Exactly. AML progresses rapidly. It's not something where you can wait weeks or even days for a doctor's appointment. Most patients end up in the hospital quickly. A complete blood count (CBC) is often the first step in diagnosis. Interestingly, many patients with AML had normal blood counts just a few months before developing symptoms. The disease can appear very suddenly.

Dr. Winer: That makes sense. But a question just occurred to me, and I'll bet it's occurring to our listeners as well: How does this happen? Meaning, what causes acute leukemia? Do we have any clues?

Dr. Podoltsev: So, we divide acute leukemias into two categories: de novo (meaning they occur out of the blue) and secondary (meaning they arise from prior conditions or treatments). Secondary acute leukemias represent a much smaller group. For example, secondary leukemias can occur in patients who previously had hematological conditions like myelodysplastic syndromes (MDS), aplastic anemia, or myeloproliferative neoplasms (MPNs). They can also occur in patients who were treated for solid tumors, such as breast cancer or lung cancer, with chemotherapy or radiation. That said, secondary leukemias make up only about 10% of cases. There are also rare patients who may have genetic predispositions that increase their risk of developing acute leukemia, but this is even less common. For the majority of AML cases, we don't know the exact cause. Certain factors—like smoking or obesity—are associated with a slightly increased risk, but these are widespread habits, and not everyone who smokes or is obese will develop AML.

Dr. Winer: And the association between having received chemotherapy for conditions like breast cancer or lung cancer and developing leukemia is limited to certain types of chemotherapy drugs, correct?

Dr. Podoltsev: Yes, exactly. For example, alkylating agents and radiation therapy are known to increase the risk of secondary leukemia, but these cases tend to arise 5 to 10 years after treatment. There's another group of drugs called topoisomerase inhibitors, such as anthracyclines, which can cause leukemia to develop much sooner—within 1 to 2 years of treatment. Still, it's important to note that secondary leukemia is rare, occurring in less than 5% of patients who receive these treatments. For instance, it's important to weigh the small risk of leukemia against the much larger benefit of treating life-threatening cancers like breast or lung cancer.

Dr. Winer: As a breast cancer doctor, I often tell patients that the risk of developing leukemia from treatments like Adriamycin (an anthracycline) is less than 1%. And as you said, for many patients, these treatments are lifesaving. That said, we're using less and less chemotherapy in cancer treatment today because of the rise of targeted therapies and immunotherapies. We're also using chemotherapy in lower doses when we do use it, so hopefully, the problem of chemotherapy-induced leukemia will become even rarer in the future. Leukemia

is also divided into a number of different subtypes. Back when I trained, we used the French-American-British (FAB) classification, which had seven subtypes of AML. How many subtypes are there now?

Dr. Podoltsev: You're absolutely right about the FAB classification—it was the gold standard for decades. But we've moved away from that system. Now, we use the World Health Organization (WHO) classification and the International Consensus Classification, which are far more detailed. These newer classifications are based on the genetic abnormalities of leukemia cells, rather than just their appearance under the microscope. Understanding the genetics of AML has allowed us to better predict prognosis and personalize treatments. For example, some genetic mutations indicate a more favorable prognosis, while others suggest the disease may be harder to treat.

Dr. Winer: That makes sense. So, this newer genetic classification system helps you both assess prognosis and determine specific treatment approaches?

Dr. Podoltsev: Exactly. Genetic testing allows us to offer targeted therapies to certain patients based on the specific mutations in their leukemia cells. It's one of the ways scientific advances have translated into real progress in the clinic.

Dr. Winer: Let's talk a bit more about prognosis. If we take all patients with AML, what's the overall prognosis today?

Dr. Podoltsev: In the U.S., about 20,000 people are diagnosed with AML each year, and unfortunately, around 10,000 people die from the disease annually. However, these are not necessarily the same patients diagnosed that year, as some patients live with AML for months or years before succumbing to the disease. Overall, we're able to cure about 50% of patients, maybe a little more. That's a significant improvement compared to a few decades ago, but it still leaves far too many patients who don't survive.

Dr. Winer: While that's sobering, it's also encouraging to see progress. I remember when the cure rate for AML was closer to 15-20%. Clearly, we're doing better now.

Dr. Podoltsev: Yes, no question. The development of new drugs in the last 10 years has certainly improved outcomes. We also have better supportive care, better diagnostic tools, and a much deeper understanding of the disease, all of which contribute to better survival rates.

Dr. Winer: Are there certain subtypes of AML that have a more favorable prognosis?

Dr. Podoltsev: Yes, absolutely. For example, patients with core-binding factor leukemias, which account for about 10% of AML cases, tend to have very good outcomes. Another group with a relatively favorable prognosis includes patients with normal karyotype AML who have mutations in the NPM1 gene. These patients often respond well to treatment and have a higher chance of being cured. And then there's acute promyelocytic leukemia (APL), which is a very distinct

subtype of AML. APL has an excellent prognosis, with cure rates exceeding 90% in most cases. However, diagnosing APL quickly is critical because it can cause severe bleeding complications if not treated immediately.

Dr. Winer: Let's talk about treatment approaches. It used to be that everyone with AML received the same chemotherapy regimen, known as "7 + 3." Are we still using that approach today?

Dr. Podoltsev: Believe it or not, the original "7 + 3" chemotherapy regimen was first published in 1973, and we're still using it for some patients. But now, we have many more options, particularly for patients with specific genetic mutations. For example, we can "enhance" the traditional 7 + 3 regimen by adding targeted therapies for certain genetic subtypes. We also have modified versions of 7 + 3 that are better suited for older patients or those who can't tolerate the standard treatment. For patients who are too frail for intensive chemotherapy, we now have lower-intensity options that can still produce good results.

Dr. Winer: You mentioned older patients. What's the median age of diagnosis for AML?

Dr. Podoltsev: The median age is around 65 to 68 years old, so AML is primarily a disease of older adults. That's why it's so important to develop treatments that are not only effective but also well-tolerated by older patients, who often have other medical conditions that limit their ability to undergo intensive therapy.

Dr. Winer: But you still see AML in younger patients, correct?

Dr. Podoltsev: Yes, absolutely. While it's less common, we do see AML in patients in their 20s, 30s, and 40s. It can occur at any age, though it's much rarer in children compared to adults.

Dr. Winer: What's the role of bone marrow transplantation in AML treatment?

Dr. Podoltsev: Bone marrow transplantation is typically reserved for patients with poor-risk or intermediate-risk disease. For patients with favorable-risk AML, like core-binding factor leukemias, we often aim to cure them with chemotherapy alone, without a transplant. For patients with poor-risk disease, transplantation offers the best chance for a cure. However, it's not without risks, so we carefully evaluate each patient's fitness for transplant and their likelihood of benefiting from the procedure.

Dr. Winer: And with bone marrow transplants, what are the typical outcomes?

Dr. Podoltsev: It's difficult to give a single answer because outcomes depend on several factors, including the patient's age, overall health, and the specifics of their leukemia. For example, we use something called the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) to assess a patient's risk of complications or death from the transplant itself. Patients with poor-risk AML who are eligible for transplant and go into remission before the procedure have the

best outcomes. On the other hand, if the patient has significant comorbidities or if the leukemia is particularly aggressive, the risks may outweigh the benefits.

Dr. Winer: What's the upper age limit for bone marrow transplant these days?

Dr. Podoltsev: There really isn't a strict age limit anymore—it depends more on the patient's overall fitness than their age. For example, the oldest patient I referred for transplant was 78 years old. He was remarkably fit; he had even run a marathon at age 75. However, patients who have smoked heavily or have other significant comorbidities often aren't good candidates for transplant, even if they're younger. Fitness and general health are the most important factors.

Dr. Winer: And when we talk about bone marrow transplants for AML, we're really talking about allogeneic transplants, where the stem cells come from a donor, correct?

Dr. Podoltsev: Yes, that's correct. In an allogeneic transplant, the stem cells come from a donor, which could be a sibling, a matched unrelated donor, or even a haploidentical donor (a half-matched donor, such as a child or parent). Haploidentical transplants have become much safer in recent years, and their outcomes are now approaching those of matched unrelated donor transplants.

Dr. Winer: One of the challenges with allogeneic transplants is graft-versus-host disease (GVHD). Can you explain what that is?

Dr. Podoltsev: Of course. In an allogeneic transplant, the donor's immune cells essentially take over the patient's immune system. These donor immune cells can attack the leukemia cells, which is what we call the graft-versus-leukemia (GVL) effect. However, those same donor immune cells can also attack the patient's normal tissues, such as the skin, liver, gut, or lungs, causing graft-versus-host disease (GVHD). The challenge is finding the right balance: we want to maximize the graft-versus-leukemia effect while minimizing graft-versus-host disease. That's the "Holy Grail" of transplantation.

Dr. Winer: And in the rare case where someone gets a transplant from an identical twin, there's no graft-versus-host disease, correct?

Dr. Podoltsev: That's correct—there's no graft-versus-host disease in transplants from identical twins because the donor and recipient are genetically identical. However, the lack of GVHD also means there's no graft-versus-leukemia effect. This can lead to a higher risk of relapse because the patient's original immune system, which failed to control the leukemia in the first place, is essentially being restored. So, while identical twin transplants are safer in terms of complications, they're not always as effective in preventing relapse.

Dr. Winer: So ideally, you want to "dial in" just enough graft-versus-leukemia effect while minimizing graft-versus-host disease.

Dr. Podoltsev: Exactly. That's the goal, and researchers are continuing to work on ways to achieve that balance.

Dr. Winer: Let's move on and talk about another type of leukemia that's seen a dramatic transformation in treatment over the past few decades: chronic myelogenous leukemia (CML). How common is CML, and what's its prognosis today?

Dr. Podoltsev: CML is diagnosed in about 9,000 to 10,000 people per year in the United States. Interestingly, the incidence of CML has been increasing over the past few decades—it was around 5,000 cases per year in the early 2000s. We're not entirely sure why this is happening. The prognosis for CML has been transformed since the introduction of tyrosine kinase inhibitors (TKIs), starting with imatinib (Gleevec) in 2001. Before TKIs, the median survival for CML was only about 4 to 5 years. Now, with TKIs, the life expectancy of patients with CML is almost the same as that of the general population.

Dr. Winer: That's incredible. So, in essence, CML has gone from being a fatal disease to a chronic, manageable condition.

Dr. Podoltsev: Exactly. We call it a functional cure—patients take a pill every day to keep the disease under control, much like managing high blood pressure or diabetes. What's even more exciting is that some patients can actually stop taking TKIs after being on them for several years. About half of patients who achieve a deep molecular response (meaning the leukemia becomes undetectable with highly sensitive tests) can stop their medication and remain in remission.

Dr. Winer: That's amazing progress. Are there other areas of leukemia research that you're particularly excited about?

Dr. Podoltsev: Yes, there's a lot happening in leukemia research right now. For AML, the development of targeted therapies has been a game-changer. Since 2017, we've had 12 new drugs approved for AML, many of which target specific genetic mutations. Immunotherapy is another exciting area. For example, CAR-T cell therapy, which has been highly successful in treating certain types of lymphoma and ALL, is now being studied in AML. In CML, researchers are working on ways to improve the success rate of TKI discontinuation and to identify which patients are the best candidates for stopping treatment.

Dr. Winer: It's an exciting time in the field of hematology. Dr. Podoltsev, thank you so much for joining us tonight and sharing your expertise.

Dr. Podoltsev: Thank you for having me, Eric.

at age 40—or earlier if they have risk factors associated with the disease. With screening, early detection, and a healthy lifestyle, breast cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and Smilow Cancer Hospital to make innovative new treatments available to patients. Digital breast tomosynthesis, or 3D mammography, is also transforming breast cancer screening by significantly reducing unnecessary procedures while detecting more cancers. More information is available at YaleCancerCenter.org.