YALE CANCER ANSWERS

Hematologic Malignancies

Care of Patients with Leukemias and Myelodysplastic Syndromes

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Welcome to Yale Cancer Answers with your hosts doctors Anees Chagpar and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital, and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert of Myelodysplastic Syndromes. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer, and if you would like to join in, you can e-mail your questions and comments to canceranswers@yale.edu or you can leave a voice mail message at 888-234-4YCC. This week, it is a conversation about myeloid malignancies with Dr. Amer Zeidan. Dr. Zeidan is Assistant Professor of Medicine and Hematology at Yale School of Medicine, and here is Dr. Anees Chagpar.

Chagpar Amer, maybe start off by telling us about myeloid malignancies, what are they and a little bit about what myeloid dysplastic syndrome is, because I understand that that is your area of expertise?

Zeidan Yeah that is correct. Basically, myeloid malignancies belong to a larger group of malignancies called hematologic malignancies. In general, we think of malignancies either as solid tumors, which are like lung cancer, breast cancer that most people are familiar with, and then there are hematologic malignancies or what we sometimes call liquid malignancies because they occur in the blood or the lymphatic organs, and those generally are divided into three big categories – the lymphoid tissue malignancies or tumors such as lymphomas and you have plasma cell disorders which originate from the plasma cells and probably the most common form of that is multiple myeloma, which I am sure many of your audience have heard of, and then we have the group of myeloid malignancies which basically occur in a type of blood progenitor, which is an early cell in the bone marrow that is called myeloid cells. These cells basically are divided into three big categories, basically their main function is to defend the body against infections such as neutrophils and cells that are carrying the oxygen throughout the blood such as red blood cells and then the platelets which are the small particles in the body that basically work to prevent against bleeding. So, those tumors arise in the progenitors or the early bone marrow cells that their differentiation leads to the formation of those mature cells. When we have a hematologic malignancy or specifically a myeloid malignancy, one of the consequences of that is that the maturation of the cells become abnormal or even stops completely and the patient will end up with what we call early or premature cells that are dysfunctional, which contribute to many of the symptoms that the patient would have. For example, because of deficiency in the neutrophils, the patients would have increased risk of infections, deficiency of the red blood cells due to the arrest or failure of full maturation can lead to anemia and its symptoms and the low platelet count problems, basically megakaryocytes, which are the cells that lead to the platelet formation, can cause bleeding issues.

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Chagpar It sounds like this is probably pretty rare, is that true?

Zeidan I would say that hematologic malignancies as a group are not that rare when you compare them to the solid tumors. But in our terms, they are actually seen quite often. For example, if I talk for example about acute myeloid leukemia, the incidence is around 4 in 100,000 people in the US, so that is around 20,000 new cases each year. Myelodysplastic syndromes are a little bit more than acute myeloid leukemia, so they are around 20-30,000 a year. The most common ones are the chronic lymphocytic leukemias and multiple myelomas, and when you add all these tumors together as a group, they constitute a big chunk of basically a major group of malignancies in general.

Chagpar When we think about the myeloid malignancies, you talked a little bit about deficiencies in production of white blood cells causing infections and red blood cells causing anemia and platelets causing bleeding, so are those the symptoms that people would have when they present with these myeloid malignancies?

Zeidan Yes. In general, we divide the symptoms in two big categories. One category is what you mentioned, the symptoms that are related to the under-production or lack of the functional capacity of the cells including the red blood cells causing symptoms of anemia like fatigue, difficulty of breathing when walking, headaches, dizziness, symptoms related to bleeding, easy bruising, bleeding from your gums when you brush your teeth and symptoms related to the recurrent infections or fevers related to the low neutrophil count. Aside from these symptoms, we have another big group of symptoms that are related to what we call hyperproliferation of the cancer cells. So you have what we call a maturation arrest, in which the cells are not maturing into the fully mature forms of the red blood cells but you have accumulation of those immature precursors, what we commonly refer to as malignant cells or blasts in the case of acute leukemia and acute lymphoblastic leukemia, which is another form of leukemia, and basically when you have hyperproliferation of those cells, they can lead to significant symptoms in their own. For example, because these cells consume some of the body proteins and excrete proteins in the blood, they can cause bleeding problems, something called disseminated intravascular coagulation, which worsens bleeding problems from the low platelet count. They can also cause increase in the secretion of uric acid, which results from the metabolism of the nuclear acids in the cells and that basically can even cause renal shutdown. Although we think of those tumors as what I mentioned as liquid tumors, they can even form masses sometimes like actual tumors. Depending on when they form, they can cause local symptoms. For example, if you have a collection of those cells resulting in a lump around the spinal cord, some people can have neurologic symptoms. If they occur in the brain area, people can have

neurologic symptoms such as headaches or double vision, or if they occur in the lung or if they occur around the heart, depending on where the accumulation of those cells occurs, they can cause local symptoms. So, in general, the presentation is variable. Rarely, we have patients who present just because they routine exam and their primary care physicians got blood counts and noticed low white cell count or low platelets or low hemoglobin and then they get worked up despite not having any symptoms. We do see that more often now that the blood work is being done more often I think than compared to the past, one of the common presentations of leukemia for whatever reason tends to be having an illness like a sore throat or just flu-like illness in which patients would be a week or two of sore throat and usually they would get a course of antibiotics and the symptoms do not improve, and eventually they would get a blood work and that shows high white cell count. That does not mean that people should freak out each time they have a sore throat or a flu-like illness, but these symptoms if they do not improve, if you have flu or a sore throat or something like that and it does not improve within a week or two or the symptoms are very severe, it is important to be evaluated because there might be other underlying problems that is causing uncharacteristically prolonged illness.

Chagpar Should people be getting routine blood work every year with their physical exam, like a blood count to see how many red blood cells and white cells and platelets have or should they really only be getting that if they have symptoms?

Zeidan Typically, we recommend that in the context of having symptoms most of the time, I am talking specifically about the CBC or the complete blood counts. The other blood work like, for example, lipids or cholesterol, those things are dictated by the guidelines and the primary care physicians usually obtain that on a regular basis, but my experience is that most primary care physicians do get blood counts at least once a year, although typically unless there are specific symptoms, there is no absolute necessity to do them.

Chagpar So, just to clarify, either patients present to their primary care doctor with symptoms and the symptoms sound like they can be pretty nonspecific, right? I am a little bit tired, I have had a flu that did not get better, I bruise easily, like those are things that I am sure our audience is sitting there thinking, I can think of a few instances where I have had that, how do people know when to get concerned and when this is just part of daily living?

Zeidan I think in general, especially acute leukemia, it is usually a major change from baseline. I think if you start for example having bruising, there are people who have easy bruising all of their life, but if somebody who does not typically have easy bruising and they

start noticing bruises that are new, they start having bleeding when they brush their gums, bleeding from the gums that has not been there before, if the symptoms of the flu or the illness are uncharacteristically severe or gets to be prolonged despite antibiotic therapy, those types of situations I think it is definitely always worth calling the primary care physician and getting some blood work done. And again, I have to emphasize here that the minority of those situations end up being acute leukemias, but because as a specialist who sees a lot of those patients, I tend to see such presentations not uncommonly, and unfortunately, it is a difficult kind of situation I would compare it, for example, as a breast cancer doctor yourself, I think when patients have breast cancer for example, they feel a lump, usually they feel it for some time and they are worried about it and they get examined and the doctor is worried about it and they get a biopsy and usually it takes several months or several weeks at least and the patient has a sense of something wrong going on and they are somewhat mentally, I do not want to say prepared, but they have some anticipation of what might be happening and they have some time to think about the therapeutic options and what to do next. One of the challenges we have with acute leukemias in general is that the patient is sick as I mentioned with a flu or what seems to be a flu or sore throat for a couple of weeks, and they present to their doctor or to the ER and suddenly their white cell count is very high and so the diagnosis is usually quite sudden and sometimes we have to initiate treatment quite quickly, even within 24 hours. As leukemia doctors, I would not say often, but we do come at night when those patients come because it is a medical emergency. There are some subtypes of leukemia that can lead to significant complications and even death if they are not handled very quickly and the diagnostic workup is started and all of that. So, you can imagine as a patient it is quite difficult to deal with all of this in terms of how your life is completely changed upside within 24-48 hours and it can be quite difficult to deal with the situation. But, I think the counter argument of that is that I always tell my patients that acute leukemias in general at least compared to metastatic solid tumors, there is a chance of cure at least. So, while it can be aggressive, it can be associated with a lot of complications. We usually have a chance at cure and we always work with the patient for that goal.

Chagpar We are going to learn a lot more about how we treat aggressive myeloid malignancies right after we take a short break for a medical minute. Please stay tuned to learn more information about myeloid malignancies and early phase clinical trials with Dr. Amer Zeidan.

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Smoking can be a very strong habit that involves the potent drug nicotine and there are many obstacles to face when quitting smoking. But smoking cessation is a very important lifestyle change, especially for patients undergoing cancer treatment. Quitting smoking has been shown to positively impact response to treatments and decrease the likelihood the patients will develop second malignancies. Smoking cessation programs are currently being offered at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital. The smoking cessation service at Smilow operates on the principles of the US Public Health Service Clinical Practice Guidelines. All treatment components are evidence based and therefore all patients are treated with FDA approved first-line medications and smoking cessation counseling. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer. For more information go to YaleCancerCenter.org. You are listening to WNPR, Connecticut's public media source for news and ideas.

Chagpar Welcome back to Yale Cancer Answers. This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Amer Zeidan. We are talking about myeloid malignancies and right before the break, Amer, you were discussing a hypothetical about patients who present with a flu, they have got a high white count and sometimes these are medical emergencies. So, I want to pick up our conversation there with a question first. It may strike people as being kind of illusive as to why the white count would be so high, I mean, if you have a cancer that is kind of cutting of the progenitors of white blood cells, how come your white blood cell count is high, why would not your white cell count be low, I thought that is why people were getting infections?

Zeidan Yes, that is a good question and what happens with leukemia is similar to other cancers, what we get is, you get an uncontrolled proliferation, so although there is what we call a cut in the differentiation, the early precursors, the cells that are earlier in their development and the stage at which there is a cutoff, they have this uncontrolled proliferation, so their number increases and the normal check mechanisms that the body has to control those, usually the body has all those check mechanisms to control the number of different cells, those become abnormal in cancer, they have what we call antiapoptotic signals in which the cells do not die or they have a pro-survival signals that basically make these cells survive more and proliferate more and not all leukemias actually have a white cell counts, those are some of the more I would say dramatic examples. We do see that sometimes, but for whatever reasons, some of the leukemias, many of the myeloid leukemias basically or almost all of them, generate basically on the bone marrow. For whatever reason, sometimes the cells tend to spill in the blood and those patients can have high white cell count, and there are situations in which actually the cells because of certain proteins in the surface of the leukemia cells that we call adhesion proteins, they can actually stay stuck inside the bone marrow and while they are not leaking into the

blood and not causing a high white cell count, there can be a lot of them inside the bone marrow and they can cause the symptoms we discussed earlier, what we refer to as bone marrow failure symptoms such as anemia neutropenia and thrombocytopenia which are basically low hemoglobin, low platelets and low neutrophils because all these leukemia cells are expanding in the bone marrow, which is the factory that makes the normal blood cells at the expense of the normal cells. So, these get crowded out and patients can have those low symptoms. While patients generally who have a high white cell counts are in a situation in which you need to make faster interventions and sometimes you need to start therapy sooner, there are types of leukemia that we used to refer to them as aleukemic leukemias, meaning that although the white cell count is not high in the blood, it is still a leukemia and this is why doing a bone marrow biopsy, which is a procedure in which we obtain a sample usually from the iliac bones and the back of the pelvis to try to examine the cells under the microscope, usually needed in most cases when we suspect an acute leukemia in general.

Chagpar But neutropenia is low white blood cells, so sometimes you can get low white blood cells and sometimes you can get high white blood cells, is that right?

Zeidan Yeah. Then the high white cell count is usually what we call blasts or the early progenitors, but the neutrophils are basically term differentiated.

Chagpar Mature cells.

Zeidan The mature cells, yeah, they get cut off and you do not make a lot of them. And we actually say even patients who do have neutrophils when they have leukemia, we usually call them functionally neutropenic, meaning that although they are a good number of neutrophils, these neutrophils do not function as they are supposed to function because of the leukemia. So, they can be still what we call immunocompromised, at risk of infection despite having a good number of neutrophils.

Chagpar When you get that complete blood count, like when you go to your doctor and they look at your white blood cell count and they look at your red blood cell count and they look at your platelets, in that white blood cell count, can they differentiate just on that simple test whether these are blast cells or whether these are neutrophils because sometimes your white blood cell count will go up because you have got an infection and because your body is making these mature cells that are fighting infections, so how do you know whether or not that is from the blasts or whether that is from the mature neutrophils?

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Zeidan Usually, most laboratories will have an automated, what we call differential count, in which using certain techniques such as what we call flow cytometry, the machine would be able to tell whether what you have are neutrophils which are what typically would happen if you have an infection and your white cell count would go up. Usually, you get neutrophils or some early versions of that, but you do not typically see blasts. Having blasts in the blood is abnormal. Usually, that will get picked up by those automated differential counts, sometimes it might be picked up as a different cell, sometimes we see what the machine would call it monocytes, but they are actually blasts. So, in those situations, this is one of the things that any hematologist is trying to do is making a smear, which basically is taking a drop of blood and spreading it on a microscope slide and looking under the microscope. The technicians would usually do that, but when there is a suspicion of having blasts, usually a hematologist would get contacted to actually look at that and depending on the white cell count and again the clinical situation of the patient, sometimes we can see the patient in a few days or the week after if the white cell count is not very high, but there are situations in which the patient will need to be transferred to the emergency room or start evaluation immediately. That is in contrast for example when you compare that with the other form of myeloid malignancies that I deal with often, myelodysplastic syndromes, which is typically manifested by low blood counts, what we call cytopenias. And that is also a common problem. It used to not get the same attention as acute myeloid malignancies largely because it occurred in mostly older people. The median age in the early 70s, and in the past until 2004, we did not actually have any type of therapies for myelodysplastic syndrome. So, historically acute myeloid leukemia gotten more attention from hematologists and oncologists than myelodysplastic syndrome, which between the two diseases are the focus of my research.

Chagpar Amer, talk a little bit about the distinction between the two, because I do not think that our listeners really understand that distinction. On the one hand you did mention that in some cases of acute leukemias, it is a medical emergency, you have got to treat now, which is kind of scary. With myelodysplastic syndromes, it is not so much, but can you draw other distinctions, how do people know what is a myeloid dysplastic syndrome versus a leukemia, how are they managed differently, what is the prognosis for each, can you tell us a little bit about the distinction between the two?

Zeidan The major form of leukemia that we are talking about here is acute myeloid leukemia because there are other types of leukemias that can affect, for example, the lymphoid cells called acute lymphoblastic leukemias, but when we talk about acute myeloid leukemia versus myelodysplastic syndromes, both of them the way I try to tell the patient to think about it is that myelodysplastic syndromes can be more of what we call a chronic type of leukemia in which depending on the severity some of the symptoms

can be progressive and severe but some of them can be mild and can take some time to develop. So, in myelodysplastic syndromes, the main feature is what we call ineffective hematopoiesis, meaning that the bone marrow is trying to produce these cells but they are dying before they reach to the functional stage. You do not typically have an increased or the same degree of increase in the blasts or basically those cells that increase the white cell count in patients with leukemia, and the distinction sometimes can be quite blur between myelodysplastic syndromes and some versions of acute myeloid leukemia. So, the traditional cutoff according to the World Health Organization classification in the bone marrow is 20% of those blasts. So, once you cross 20% or plus, typically you go into the area of acute myeloid leukemia. While if you have less than 20%, generally that goes along the lines of myelodysplastic syndromes, although that cut off for management purposes is not something that is an absolute for us. Sometimes, for example the treatment of in general those malignancies go into two different or two large categories, one of them is intensive chemotherapy, in which the patient will need to be hospitalized for significant amount of time, get intensive chemotherapy and wait until their blood counts go down and then recover, and that type of treatment is something we typically do for acute myeloid leukemia. There is another form of treatment called hypomethylating agents such as azacitidine or decitabine, and we generally refer to that lower intensity therapies because they can be given outpatient, they are typically either an injection under the skin or an infusion over an hour and they are given for 5-7 days basically each 28 days, so those treatments depending on the age of the patient and their other illnesses, as I mentioned most of those patients are older and doing intensive chemo can be quite difficulty, so sometimes for myelodysplastic syndromes and some forms of leukemias, we do those lower intensity treatments regardless of the number of the blasts in the bone marrow. So, it is usually a matter of discussion in terms of what are the goals of the treatment and taken into consideration not on the factors of the tumors such as percentage of those blasts and the cytogenetic changes, which are the changes in the chromosome – the genetic factors that drive the leukemia, but we also take into consideration the patient's own wishes, what are their goals. Usually, in younger patients, the goal is to try to go for a cure even if the treatment has initial toxicity. While if the patient is much older and the disease is quite difficult to cure, the goal might be to try to palliate the symptoms and improve their quality of life and try to prolong their survival, but sometimes cure can be quite difficult in those situations.

Chagpar It sounds like the boundaries are fuzzy between acute myeloid leukemias and myelodysplastic syndrome, is that right?

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Zeidan I would say for some cases, it is quite difficult to make the distinction. There are cases that are more straightforward when you have, as I mentioned a lot of blasts with a high white cell count, that tends to be clear-cut, or when you have myelodysplastic syndrome in which the number of the blasts is relatively low like 5-10% or less than that. But when the blast count is close to 20, it becomes a matter of just what do you call it, but ultimately the treatment might not change. So, there are patients who have let us say 15% which are technically categorized as myelodysplastic syndromes, but if they are younger, sometimes for those patients, we would give them intensive chemo, the type of chemo that you would give for an acute myeloid leukemia, and there are patients who cross that 20, let us say 30% of blasts, but they are older and they have other medical problems, and in those situations, those patients we might consider those lower intensity treatment and not intensive chemo because the chance of complications and even dying from the treatment can be quite high.

Chagpar In terms of the nomenclature, it sounds like when somebody hears leukemia, we think, oh my God cancer, I am going to die. When we hear myelodysplastic syndrome, it sounds so much nicer, it sounds like it is not a malignancy, so is it a cancer really?

Zeidan Yeah, it is definitely a cancer, that is actually a great question and each time I get to talk about MDS, I always emphasize this point that not only the patients get educated by that but some of the oncologists in the community think of it because it is called a syndrome or a preleukemia or anemia. I think myelodysplastic syndromes get underestimated in terms how aggressive they can be. One of the figures that I usually put in my presentations is basically a presentation of the survival curves for patients with myelodysplastic syndrome, according to the classification. We have a classification called International Prognostic Scoring System. It goes from low intermediate I, intermediate II and high, and those at the high level, they are almost as bad as having stage IV lung cancer. So, the median survival for those patients without treatment is less than 0.4 years, less than 4 months. So, myelodysplastic syndrome can be quite difficult, can be quite aggressive and very aggressive treatment including allogeneic bone marrow transplantation can be required in those cases and should not be underestimated and because it is a rare disease, referral to experts in that is usually a very good idea.

Dr. Amer Zeidan is Assistant Professor of Medicine and Hematology at Yale School of Medicine. We invite you to share your questions and comments. You can send them the to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC, and as an additional resource archived programs are available in both audio and written form at YaleCancerCenter.org. I am Bruce Barber, hoping you will join us again next Sunday evening at 6 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's public media source for news and ideas.