YALE CANCER ANSWERS

Hematologic Malignancies

Care of Patients with Leukemias and Myelodysplastic Syndromes

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Welcome to Yale Cancer Answers with Drs. Anees Gore and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week it is a conversation about myelodysplastic syndrome with Dr. Amer Zeidan. Dr. Zeidan is an Assistant Professor of Hematology at Yale School of Medicine and Dr. Gore is a professor of Internal Medicine in Hematology at Yale and Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore Myelodysplastic syndrome is a lot of syllables, what does it mean?

Zeidan Myelodysplastic syndromes are actually a group of diseases. It is not only one disease and I should probably clarify that it has been officially recognized as a form of cancer, and many patients struggled for a long time getting different information from different healthcare providers about whether this is a cancer or not. For a long time, it used to be called preleukemia, which we now understand based on a lot of studies looking at the genetics of the disease that it is actually a form of cancer and a form of leukemia. The way I usually describe it to my patients is a form of what we call bone marrow failure, so when we think about any organ in the body, when it fails, it basically stops performing what it is supposed to do and I tell them to think of the bone marrow as the factory that makes all the blood cells and when that factory fails, you end up with low blood counts, basically employees in the factory are all doing the wrong function and all these cells come up looking bad and looking abnormal, so this is the part of the myelodysplastic, and the dysplastic means that those cells look abnormal and you can think of it most of the time as a form of chronic leukemia, meaning some patients can live with it for a long time, but some patients do progress to more aggressive forms of the disease.

Gore How would I know if I had this myelodysplastic syndrome?

Zeidan The most common way of being diagnosed with this form of cancer is that it usually includes some nonspecific symptoms related to this bone marrow failure. When the bone marrow stops making the red blood cells, patients can get anemia, they have symptoms of anemia which include low strength, shortness of breath with walking, feeling generally of not being well, symptoms of bleeding can occur when you have low platelets, those are the small cells that help our body to prevent bleeding, when those go low, some patients can have bleeding. Some patients can have recurrent infections from the low white cell count; those are the soldiers in the body against the infection, so patients can have recurrent infections. However, with the advances in medicine in general and wide use of routine blood work for many conditions, we are seeing more and more patients who present without any specific symptom, just low blood count and the way we usually make the diagnosis is by doing a procedure called bone marrow biopsy which is a sample that we take basically from inside the bone, usually from the low back and this allows us to examine the

cells under the microscope to study the genetic makeup of the cells and then determine not only that the patient has myelodysplastic syndrome, but also understand more about what is the expected course and how is the patient likely to do over time.

Gore So I have gone to my doctor, he has found that I have low blood counts or something like that and then I am referred for a bone marrow test, is that right?

Zeidan Correct.

Gore Is that a big deal, this bone marrow test? It sounds kind of scary.

Zeidan Each time I tell patients it sounds worse than it is, they tell me, well did you have one, and I did not have one. It is difficult for me to say that for all patients it is a simple test, but I would say for the vast majority of patients, it is an outpatient procedure. It is done usually with just local numbing medication over the bone and it usually takes less than half an hour for most patients. So for the vast majority of patients, it is pretty straight forward, it is one of the safest procedures that we do in medicine because the risk of complications which generally could be either infection or bleeding are generally very low and it is like any other procedure when it is done in places where the providers are more experienced, and I think that usually improves patient's experience. I would say for the vast majority of patients, it is quite straight forward, very few patients would require general sedation.

Gore For our listeners, I have actually had a bone marrow test, but not the biopsy part, just an aspirate part and I have to say that while I would not want to go through one every day, it was really pretty much a snap, I would have to say the uncomfortable part lasted, I do not know, about 20 seconds or something like that.

Zeidan Yeah, I would agree. I would say most of my patients who undergo it, usually tell me this was way easier than it sounded when we described it.

Gore So you do this bone marrow test and the pathologists help you make this diagnosis, and you find out some of this biological information that you are looking for, then what happens?

Zeidan That is a great question and some of my research in that area focused on understanding how we can translate not only the biologic or what we call the morphologic features, how the cells look in the bone marrow, into information that can help us guide the decision making for patients and how we counsel them about what to expect with the disease and what types of treatments to recommend. This test has a wide range of implications and what we do with the information. I think one of the areas that we are still understanding and have done more research on is how to best use this data to direct decisions regarding therapies. So we have some information that we can get from blood tests as well as the bone marrow biopsy. We look at the type of dysplasia which as I mentioned how many of those blood cells are affected by it and how badly they are

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affected. We look at the chromosomes within the cells and we look at the blood counts. In addition to that, more recently, we discovered that even what we call genetic alterations at the level of the individual genes, those also can affect not only how the patients will do over time with the disease, but also they are opening the door for therapies that can directly impact the disease, what many people refer to as precision medicine, which is basically delivering specific therapy tailored to that the patient's particular disease.

Gore Since you are saying that this disease has this genetic feature, does that mean it is an inherited disease, it runs in the family?

Zeidan That is a great question and one of the most common questions that comes up when we have the first encounter with many of our patients. I would say for the vast majority of patients, there is no specific reason why they developed it and this is what we call idiopathic which is a term that we often use in medicine when we have no idea what the disease came from.

Gore It sounds better than I don't know, right?

Zeidan Exactly, it is another word for I don't know. Usually we think of it as some kind of interaction between what we call genetic susceptibility that your DNA makes you more susceptible to certain diseases, the same way some people can develop heart problems or lung problems, and then interaction with environmental factors. However, in a small subset of patients, I would say around 20%-30% of patients there are usually identifiable factors which usually either include previous cancers for which they have received chemotherapy or radiation and that can damage the bone marrow and over time can lead to the development of this disease. Sometimes patients could have environmental exposures which could include either some form of radiation or, sometimes occupational exposure, such as benzine exposure. All of these can predispose to the development of the disease. Some patients do have a genetic component in the sense that it is inherited, however, I would say this is a very small minority of patients, those are generally the ones who develop the disease at a younger age and it tends to be associated with other organ manifestations. Some patients have what we call skin manifestations or bony manifestations and usually you have more than one member in the family affected. For most patients with MDS, it is usually one member in the family and I usually assure most of my patients that this is unlikely to affect their children because most of the time, as I mentioned, it is not directly inherited.

Gore So these abnormalities in the genes that you are talking about; they have been acquired at some point after birth, is that right?

Zeidan Correct and it has been an extremely interesting era in science that not only do we now understand that damage over time leads to accumulation of these changes that eventually

manifest as myelodysplastic syndrome or even other forms of blood cancer, but now we can even demonstrate

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that in many patients they have some alterations even before they had any form of recognizable disease, so this can happen over many years before the patient presents to the doctor.

Gore How would you find it then?

Zeidan This was done in several ways, one of them was when patients underwent studies looking at, for example, cardiovascular risk factors which are diseases that occur in the heart, or other forms of registry data in which they donated blood cells, and subsequent to that, a small group of these patients, we are talking here about a very large number of patients over a very long time, some of them did develop myelodysplastic syndrome and then the researchers went back to those stored cells and looked at them and they found that many of these patients did have some abnormalities that proceeded that in the same way it was demonstrated more recently that some patients who have one cancer and undergo radiation or chemotherapy, had some cells collected at that time and subsequent to that, when some of these patients did develop myelodysplastic syndrome, they went to the original samples and again they found some of these genetic alterations that has been associated with the development of myelodysplastic syndrome which is in my mind is actually very interesting because not only does it open the door for trying to identify some of those patients who are likely to develop the disease over time, but also it might allow us to have opportunities at trying to intervene early on before myelodysplastic syndromes manifest, so that in some way it is a preventive strategy which would be very important because as we will probably talk about later in the show the treatment options for myelodysplastic syndromes are generally limited and therefore, a preventive strategy would be ideal.

Gore How good are the treatments that you have for these sets of disease?

Zeidan The way we think about myelodysplastic syndromes in general is we use different tools in which we put the different clinical and genetic features of the patient to try to come up with what we call risk stratification. This is a big word, but what it essentially means is that we try to predict their expected survival and their chance of progression to an acute form of leukemia over time. So when think about that, we generally group the patients into two large groups. One of them is what we call lower risk and the other group is higher risk patients and the goals of therapy for these two groups are very different because in lower risk patients, unfortunately so far we have not identified any treatment that can prolong survival. Our focus in general is to improve the quality of life or maintain it and to try to reduce the transfusion needs and generally these patients, if you lump them together, on average they live somewhere between 3 to 7 years depending on the specific group, but this is what we call a median number. So each time I tell a

patient about these numbers, I always tell them that this is the number at which half of the patients are expected to survive, but there are patients who live much longer, there are patients who live much shorter.

Gore That is very interesting and a little bit sobering if that is the survival of the better risk

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patients. I will pick this up after our break, but right now, we need to take a short break for medical minute. Please stay tuned to learn more information about the interesting cancer called myelodysplastic syndrome with Dr. Amer Zeidan.

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Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore and I am joined tonight by my guest, Dr. Amer Zeidan. We have been discussing a group of bone marrow disorders, known as myelodysplastic syndrome. Amer, before the break, you were mentioning that you look at various features of the patients blood counts and bone marrow features and biological studies you have gotten and you classify them into either low risk group of patients where you don't feel as I understand that the treatments improve survival but are aimed at improving blood counts and quality of life, do I have that right?

Zeidan Correct yes.

Gore What about the other group, which I guess would be high risk?

Zeidan Yes, around two-thirds of the patients belong to the lower risk group and around one-third of the patients belong to the higher risk group. However, we have to keep in mind that this is what we call dynamic scoring, some of these lower risk patients over time can progress and then they can become a higher risk group. When we think about the higher risk group in general, those are the patients who do the worst when they have this form and these are patients in whom the disease really almost behaves like a form of acute leukemia in some patients, in the sense that the survival without intervention is quite limited. Studies have

shown that without active treatment, meaning without treatment that specifically targets the disease, the survival of those patients could be limited to less than a year and this is again part of why, I think it is very important to get the message out in the community that myelodysplastic syndromes are real cancer, they should be identified, and they should be adequately treated when possible. For a long time, there was this analytic approach about diagnosing myelodysplastic syndromes, but most patients with myelodysplastic syndrome are actually older patients so the median age, basically the age at which most patients present, is in the mid-70s and many physicians used to not even perform these

17:58 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0318-Podcast-Zeidan_329744_5_v1.mp3

bone marrow biopsies on those older patients because they were saying for a long time we did not have any good therapy, so why should I bother with getting a bone marrow biopsy and that definitely affected the outcome of some of these patients because I do think currently we have some good therapies and I think we should really try to diagnose the disease in most older patients who have anemia because anemia is always a manifestation or a result of something else. Anemia is not a disease by itself in the sense of being a disease, it is usually the result of another process and I think trying to identify that process whether it is a form of bleeding from the gut or is it some other form of blood cancer, is very important because this is how you make the decisions about the therapies.

Gore So it is not normal for older patients to just become anemic because they are older?

Zeidan Correct and that is actually a very important message.

Gore I think a lot of patients seem to think well I have always been anemic, you heard that a lot, right?

Zeidan Correct and even some physicians in my experience assume that as you get older you are supposed to get anemic or it is not unusual to be anemic. In my experience if you dig enough most patients will have some identifiable and very often correctable factor underlying their anemia and again anemia, for some patients, might not be producing all of the symptoms when they come to you, but I can tell you many of my patients who did not think they have a lot of symptoms once you fix that anemia, they said, I was really having symptoms I did not realize that I was feeling so tired and now I feel more energetic and more fresh and all of that. So I think some of that can definitely be underestimated by not only the physician but by the patients as well.

Gore When I first got glasses, eye glasses at the age of 40, and I didn't have a big prescription, but I had some astigmatism and I had not realized how out of focus all the trees were that I could not really see the individual leaves and all of a sudden I was like looking in 3 dimensions, with a kind of rather minor improvement, but because you do not know how out of whack you are until you become normal, right?

Zeidan Yeah and I think that is important for patients to realize that there should at least be some kind of investigation into the cause of it and ultimately, there should be some consideration of sending the patient to a blood doctor if the cause of the anemia, especially in the older patients, is identified because again having anemia is not a normal part of ageing. I think that is important to get out. So for those patients who get diagnosed with higher risk MDS, that high risk group, the treatment options for a long time had been quite limited. They only included basically going for a bone marrow transplantation which can lead to cure in some patients, however, as a form of transplantation, it is quite a risky procedure because those patients, as we mentioned, most of them are older, they often have other diseases in their lungs, in their heart and there are generally only a few patients that would tolerate bone marrow transplantation very well and it always comes to my

21:20 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0318-Podcast-Zeidan_329744_5_v1.mp3

mind because each time I write a paper or anybody quotes research about myelodysplastic syndromes, they always talk about how bone marrow transplantation is the only way to treat it, but part of our research effort has been actually trying to see how often do we perform transplant on those patients and what we found is that among older patients, who are the ones who are mostly affected with this disease, less than 5% and I would say less than even 2% of patients with higher risk MDS do undergo bone marrow transplantation.

Gore 2% when that is the curative therapy?

Zeidan Yes and it is shocking to me how this gets emphasized all the time. I think it is very important to think about it, but in realistic terms it is mostly used for the younger patients, for the patients who are in good shape, but for the vast majority of patients with myelodysplastic syndromes, it is something either that is not recommended because of their age and because of their other problems or because sometimes they cannot identify a donor despite all the advances in identifying donors and sources of bone marrow stem cell transplant these days, but sometimes the patient himself when they are counseled about the possible side effects and all of that, they refuse it. I would say the vast majority of patients do not undergo this bone marrow transplantation and that leaves most of these being treated with what are called palliative measures. What we are trying to do is extend their survival and improve their quality of life by reducing their needs for transfusions. The most active form of therapy currently used for those patients are a group of drugs called hypomethylating agents, they are two of them that are approved in the US, one of them is called azacitidine and the other one is called decitabine. Those drugs have been shown to improve the quality of life and to reduce the transfusion needs and to hold the progression to acute leukemia in some patients with myelodysplastic syndromes. Large randomized studies which are our best evidence in medicine, in genal have shown that only azacitidine prolongs survival in patients with MDS, however, it is one of the features that I think gets highlighted all the time about how azacitidine changed the landscape of myelodysplastic syndromes. While I think it is a very good drug because definitely some patients do respond to it and some patients can have prolonged remissions from the disease, if

you look at the numbers, only less than 15% achieve the ideal response, what we call complete response. Less than half of the patients achieve any kind of response meaning that more than half of the patients do not achieve a response and we have no real way of identifying which patients are going to respond or not and this therapy usually takes several months to fully result in benefits which means that for many patients you are keeping them on months of therapy that is not going to work and this therapy does not usually hold the patient for a long time. If you look at most patients, usually even if they respond, the small group of patients who respond do not usually have a response that lasts more than 12-15 months and the survival if you look at the group, the survival prolongation is really 9 months if you look at the two groups of patients who received azacitidine versus those who received what we call conventional care which are the other things we used to do before we had hypomethylating agents available. My research is focusing on how we can improve the outcome of these patients and looking at the real life setting to see these how therapies work in real life. If you think about clinical trials we are choosing the

25:35 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0318-Podcast-Zeidan_329744_5_v1.mp3

strongest patients who are able to pass a very stringent list of qualifications to go into trial, which do not really match most of what we see in the clinic and when we look at the benefit of hypomethylating agents among patients in the real life sitting using large databases, we find that these drugs significantly underperform and we presented some of that research at the last American Society of Hematology meeting by which we showed that not only the median survival or basically the average survival, if you put all these together is less than 2 years, and that was reported in the largest trial, but a lower percentage of patient's have any kind of sustained response overtime. I do think that the way going forward is to continue to improve outcomes of patients by trying to get them into clinical trials. I think we have a good therapy with azacitidine and decitabine, but I think it is very important that we continue to try to improve those therapies because there are significant issues currently with them.

Gore So how does one do that? What will you do when your best drug is affecting maybe 40% or 50% and as you pointed out, underperforming potentially outside of the strict confines of a clinical trial. What kinds of thinks were exciting to you in clinical research, I know you mentioned you were just presenting at this international meeting. Is there anything exciting going on?

Zeidan That is a great question. For a long time, many of the blood cancers were traditionally treated with what we call chemotherapy. When you talk to most patients about cancer in general, the word chemotherapy comes to their mind and they think about nausea, hair loss and these are the things that usually come to their mind but I think oncology has been changing in amazing ways in the last 10 to 15 years. We have a lot of focus in two big groups of therapies currently. One of them is called targeted therapies and the other group is called immunotherapies. So those do not give you the traditional chemotherapy side effects such as nausea and hair loss and significant organ damage, those were generally by two big mechanism, so the targeted therapies are the small molecules or small, basically agent drugs, that are designed to attack a

specific alteration in the myelodysplastic syndromes. For example, in acute myeloid leukemia which is a related disorder we have two of these agents that are in advanced clinical development, one of them is called FLT3 and the other one is called IDH 1 and 2, so those genetic alterations lead to changes that subsequently cause the disease and we have specific drugs that inhibit them. This is an acute myeloid leukemia, so those abnormalities happen in a small subset of patients and we currently have trials that combine drugs, oral drugs, that inhibit these specific alterations and we have trials where we combine these drugs with azacitidine. I think the platform that I generally think is the best is to combine azacitidine with another drug. In addition to the targeted therapies, we have the immunotherapies which is an area of special interest of mine. So many people think of the immune system as a way of defense against infections, but the immune system is actually our most efficient way of defending against cancer. The reason why cancer develops in most patients is because the immune system at one point stops recognizing these abnormal cells, so when our DNA damage happens every day, the cells take care of it. If the cell becomes abnormal, the immune system would take care of it. At one point, the immune system stops recognizing that damaged cell and that damaged cell can proliferate and become a cancer and there has been a lot of research on why does that happen and how we can stimulate the immune system. The commonly used term

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is basically removing the breaks in the immune systems, so that it attacks the cancer cells. This has been done by several mechanisms and it is already showing amazing results in solid tumors such as skin cancers, melanoma, and lung cancer and we are trying to do the same thing in blood cancers. We have already seen some good results with those group of drugs, the fair set of drugs that came were called immune checkpoint inhibitors and they have resulted in amazing results in solid tumors, in some blood cancers, such as a form of lymphoma called Hodgkins lymphoma and currently we are doing that in our patients with myelodysplastic syndrome combining these drugs with hypomethylating agents along with other forms of immunotherapy.

Dr. Amer Zeidan is an Assistant Professor of Hematology at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on Connecticut's Public Radio.