Yale CANCER CENTER answers

WNPR Connecticut Public Radio

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Discussion of Hematological Malignancies Part II

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas and Dr. Chagpar is Associate Professor of Surgical Oncology and she is a Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. 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, you will hear Part 2 of Dr. Chagpar's conversation with Dr. Steven Gore. Dr. Gore is the new director of hematologic malignancies at Smilow cancer hospital and here is Anees Chagpar.

Chagpar Steve this is part two of our show on hematologic malignancies, so let's go back and refresh everyone's memory if they missed our first show, although I am certain that our loyal listeners would never miss our show, but just recap for us again what myelodysplastic syndrome is and how it is diagnosed.

Gore Myelodysplastic syndrome is a kind of what we call a chronic leukemia or bone marrow disorder where the blood cells tend to be low and people often will have low red cells causing anemia, low infection fighting white cells and low platelet counts. They are often diagnosed based on those low blood counts and any symptoms that have derived from those low blood counts and unfortunately overtime, the disease tends to get worse and often eventuates in a more serious or more aggressive kind of leukemia that we call acute leukemia.

Chagpar Let me get this straight, we went from a type of chronic leukemia to an acute leukemia?

Gore In nomenclature anyway, which means we went from a more chronic disease to a more aggressive form of the disease.

Chagpar Or as you called it last time, a very, very, very bad myelodysplastic syndrome?

Gore Exactly.

Chagpar So a patient is diagnosed with this and the last time we were chatting you mentioned that it is really important to understand what a patient's goals are when you try and treat that patient. So go back and tell us a little bit more about how that decision making happens?

Gore We first get all the prognostic information we can based usually on the patient's bone marrow tests to help that patient understand what the likelihood of progression of their disease is over what period of time, because that can frame for them how aggressive we may need to be to help them achieve their goals now. If they are 80 years old, their goals may just be, give me a good quality of life to be with my family as much as I can and I have accomplished a lot of what I wanted to accomplish and I am not really up for doing some major, dangerous thing, or you may have

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a 60 year-old who would like to be cured, because they would like to live their normal life expectancy if possible and everything in between. So we talk to people about their disease. What is realistic to expect? What treatments are available? What kinds of research studies might be available? How those may impact their decision making and then as a team, the patient and I and hopefully their family will come up with the plans specific for that patient.

Chagpar On this show, as well as on our previous show, you used the word, cure. Can cancer really be cured?

Gore Well the cancers that I treat can.

Chagpar Tell us a little bit more about that.

Gore There are some acute leukemias that can be cured with an auto stem cell transplant. We call them curative leukemias and there are a percentage of them that will be cured with the first set of chemotherapy treatments that are offered and delivered. Then there are diseases like myelodysplastic syndrome where we have therapies that can help the blood counts, help the quality of life, but if left as the only therapy will ultimately lead to relapse of the disease and progression of the disease and myelodysplastic syndrome, therefore, can only be cured with a stem cell transplant, but of the patients who get a stem cell transplant, there is a percentage of them who will be cured, meaning the disease will never come back and they can except a normal life.

Chagpar That sounds really great. Let's talk about what exactly a stem cell transplant is and how that works and that is where we left off our last conversation.

Gore Right.

Chagpar Let's go back and say you have a patient and you have gone through talking about their life goals, you have looked at all of the prognostic factors and you think that this is a patient who really can be cured and they say to you, Dr. Gore, if you cure me this will be the best thing ever. Then what happens?

Gore Then we need to choose a therapy, which can get them ready for transplant, and to bring them into some kind of remission and typically that will involve a drug called azacitidine or a similar drug called decitabine, but many such patients are actually eligible for a National Clinical Trial, for example, which are aimed at increasing the number of people who will respond to these drugs by combining them with other drugs. So if there is a clinical trial available for such a patient, we would certainly offer that clinical study and see if that would be something that we would be interested in enrolling in, but at any rate, whether on or off a clinical trial, they will receive several months of treatment usually because with an azacitidine based therapy, it may take 4 to 6 months in all to know if it's working or not.

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Chagpar So these clinical trials, is this instead of the stem cell transplant or is it instead of the azacitidine to get into a remission so that you can have the stem cell transplant?

Gore This is to help the person get ready for transplant and it usually will involve active drugs that often will include azacitidine either alone or in combination with something which might make the azacitidine work better, for example. We usually would not offer what we call a phase I drug, a new drug where we have a hunch it might work and we are looking to see if it is toxic or not. We would not offer that to such a patient at this point because we are really trying to get this patient ready for transplant and feeling as good as they can, as fast as we can. So it would not really take a riskier option.

Chagpar I think that's a good point that I want to pick up on because I think a lot of our listeners may be confused about what the difference is between the different phases of clinical trials. You mentioned that you would not do a phase I or riskier drug, but you would still do a clinical trial, so help us to understand what that means?

Gore It is interesting because when I started working on myelodysplastic syndrome in 1993, there were no drugs approved for the treatment of myelodysplastic syndrome and the patients with myelodysplastic syndrome were basically supported with blood products, transfusions, and if they could get a stem cell transplant, which was much riskier in those days, they might be lucky, but most patients died of their disease. Now there was already a National Clinical Trial that had studied this drug azacitidine and the patients who were enrolled on that study were randomly assigned to either azacitidine or just blood transfusion support, and then the patients that got blood transfusions support only, if their disease was not getting better by itself, which of course it never did, they were able to get azacitidine. So everyone at the end of the day got azacitidine. So that was one of the most important clinical studies that was done in myeloplastic syndrome which definitely demonstrated that it was an active drug, even though there had been some smaller studies, which suggested it probably would be and remarkably that study was run by the National Institutes of Health. There was no drug company sponsor for this drug. The NIH was making the drug as there was no pharmaceutical sponsor and a company named Pharmion was created and took those data that were developed by the NIH and actually brought the drug to market. So clinical trials are so important because if people in the 1990s hadn't been willing to go on that trial, which was risky because half of them were not getting the study treatment for a while, that must have been awful, but if they had not been willing to do that, we would not have that drug today. So clinical trials are really so important because that is how we develop active treatments and it has been shown that the patients who are enrolled on clinical trials get better care even at great cancer centers than the patients not on clinical trials because the clinical trial protocol pays such close attention to every little thing that the doctor and the research nurse and the nurse practitioner,

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and pharmacist have to do. In some way, it standardizes care to the very best level possible, even at places like Smilow, which delivers great care. I know people are afraid of clinical trials, are worried they are going to get a little bit of placebo, but most clinical trials do not have placebo or when they do, it might be a placebo in addition to a standard drug.

Chagpar The other thing is that some clinical trials like the ones you are talking about now are not necessarily the first time this drug has ever been tested, and oftentimes these are, is active drug A better or worse than active drug B, is that correct?

Gore Or is this drug effective in 40% of patients or 70% of patients, or can we make this drug by tweaking it with something else, go from 40% responders to 70% responders. In fact the current national trial for myelodysplastic syndrome, which we hope to be opening up at Smilow in the next few months, actually has a three-wave randomization, a third of the patients will get standard azacitidine, which is great because that is what we give them anyway, a third of them get azacitidine plus another FDA approved drug called lenalidomide, the combination looks very effective in small studies, and the other third gets a combination of azacitidine with a third FDA approved drug called vorinostat, again the combination in small studies looks much more effective, but we all know that when we take these promising combinations into larger studies, sometimes we find out that it is not as good as it looks or maybe it is better than it looks. So we really encourage patients to go on studies.

Chagpar Because that looks like it is a win, win, win situation.

Gore Exactly there is no bad choice.

Chagpar No matter which group you are in.

Gore Exactly.

Chagpar You are getting a drug that you would normally get and that we know works, you just may be getting an additional drug that may make it work even better.

Gore And you are contributing to the next generation of patients who can look back at you and say, I am taking this combination because a lot of people took the chance and ensured that it was better. Because at that time, they did know, that is so important.

Chagpar We are back to our patient who we are now going to treat with curative intent. They decide to do the clinical trial, great choice, and they go into remission. How do you know that they are not in remission already from the stem cell transplant? Is it a certain period of time or are you looking at blood counts or is it when it is convenient? How does that work?

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Gore The nice thing about myelodysplastic syndrome for patients is they do not really need a doctor to tell them how they are doing because they know if they are getting red cell transfusions or not. They always ask what the blood counts are and they can see when things start to get better. They also know when things are getter worse, unfortunately. So it is not like an advanced cell tumor malignancy where you do not know what that lesion in your liver is doing until that dreaded CAT scan and everybody is worried about the CAT scan as well they should be, or the PET scan. Here you pretty much know if your blood counts are getting better or not because even if your bone marrow looks better and we repeat that terrible bone marrow test we talked about, usually after about four or six months, we look at that. Even if the bone marrow is looking better, if the blood counts are not getting better, then it is not a great response. We really want to see the blood counts get better whenever possible and again that is something that the patients know about. Oftentimes they come running to me and say, Dr. Gore, my platelet count is 90,000 and I think that is good. Well you know it used to be 30,000 and normal of course is 150,000 and I say, of course that is great. Let us hope the next test is just as good. Then, after a month it may be 150,000 and that patient we know is doing well.

Chagpar How do you know when it is the right time to do that stem cell transplant? I mean how good do people's counts need to be? Do they need to be back up to normal? And the second part of that question is can you take all of these drugs to get into remission for as long as it takes?

Gore Well you can, but there is diminishing return after a while and so about 70% of the patients who are going to have a great response to azacitidine based therapy will do so within the first six months. Then there is another 20% that will develop it within the first nine months and then there is a tiny little tail that will take 12 months. So you cannot just keep going and going. If you are not getting where you need to be after a certain period of time we probably need to regroup and choose another treatment.

Chagpar Well we are going to regroup right after we take a break for a medical minute. Please stay tuned to learn more information about hematologic malignancies with our guest Dr. Steven Gore.

Medical Minute *The American Cancer Society estimates that over a 1000 patients will be diagnosed with melanoma in Connecticut each year. While melanoma accounts for only about 4% of skin cancer cases it causes the most skin cancer deaths. Early detection is the key. When detected early melanoma is easily treated and highly curable and new treatment options and surgical techniques are giving melanoma survivors more hope than they have ever had before. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for melanoma. The specialized programs of research excellence in skin cancer grant at Yale also known as the SPORE Grant will help establish national guidelines on modifying behavior and on prevention as well as identification of new drug targets. This has*

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Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar, and I am joined today by my guest Dr. Gore. We are discussing hematologic malignancies, specifically myelodysplastic syndrome and right before the break, Steve, we had our patient, our patient was on a clinical trial and they took their therapy and they started to see their blood counts getting better. At what point do they then get that transplant?

Gore We assess their response in the blood and in the bone marrow usually after four to six months and again we may repeat it if they need a little more time, but as soon as they have their best response and we have reduced those bad blast cells in the marrow to a normal level, now we need to have thought about what the transplant is going to look like way before now because we need to know who the donor is going to be and depending on what kind of transplant center you are at there may be different kinds of donors. We usually look first to siblings and we look for a full match in a sibling and this is done through blood testing. You may look for an unrelated donor through the National Marrow Donor Registry. Many places will actually use mismatched family donors. We hope to build that at Smilow in the next year or two. That is a very exciting area of research and sometimes even stem cells are derived from donated umbilical cord blood from placentas, from newborns. That is something we are not yet doing at Smilow, but we will probably be building it in the near future as well. So based on what is available for the patient, whether they have siblings or not and whether they are matches or not, we need to have all those ducks in a row well ahead of time.

Chagpar Let's talk a little bit about that because I know that many of our listeners are probably very aware of the organ donation shortage and so for all of the listeners out there, if you have not signed your organ donation card on your license, it really does make a big difference. Does bone marrow transplant work the same way for unrelated donation?

Gore No, so bone marrow donation is done with living people not from people who have been in an accident or something like that you often see for kidney transplants and so on. People can choose to be potential donors on the National Marrow Donor Program, and often the easiest way to become a marrow donor is to go to your local Red Cross, and there are other ways, you can go to bethematch.org. And I think the website marrow.org tells you different ways to donate blood so that your tissue typing will be listed on the registry and you will then be searched whenever somebody is looking for a donor. Again, we usually first go to first degree relatives and then if they do not have a donor, we will look at the registry.

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Chagpar So the first thing is, be nice to your siblings.

Gore Always.

Chagpar Because they are going to be the first choice and then next it is on to the bank. You mentioned a couple more novel ways of getting marrow. Tell us a little bit more about those and what you are doing at Smilow to rev up that whole system.

Gore Unfortunately many people, or even the majority people, will not have a sibling donor and not everybody can find a great match on the marrow donor registry, especially people of non-European mainstream ethnic groups, which will include African Americans, Ashkenazi Jews, anything besides your most northern European descents. So there has been a large area of research, some done at my previous place of employment, Johns Hopkins, looking at making more unusual transplants very feasible and at Hopkins, I was privileged to be a part of a research team that developed transplants with half matched related donors and almost everybody has a half matched related donor either a parent or a child, or half matched sibling and it took me a long time before I would send some of my patients for that Phase I transplant. I would send them out to Seattle for a matched unrelated donor honestly because I felt that this was too risky, but thank God there were patients who were willing to do that risky stuff because I have to say I am a total believer because we can find a donor for most patients very rapidly and we are hoping to get that kind of transplant going at Smilow in a short period of time. We are currently searching for a new head of transplant who will hopefully have those interests and will get that moving.

Chagpar So you can use people who are not an exact match?

Gore Correct.

Chagpar And how does that work? Do they have worse results?

Gore No, the results are at least as good but first of all people should understand that a bone marrow transplant is not like an organ transplant. In a kidney transplant you take the kidney and you implant it and people always think, even some doctors think, that we must be taking one of these giant needles we talked about and injecting marrow into the bones. It is not like that at all. The bone marrow transplant actually is a series of chemotherapy or chemo and radiation treatments that get the donor ready to receive stem cells and then the stem cell product, whether it is from blood or bone marrow or umbilical cord blood, is actually infused like a blood transfusion, and miraculously, the new stem cells circulate around the blood and find their way into the appropriate places in the bone to set up shop like planting seeds in a garden and over the course of a couple of weeks, they grow. Now my colleague Dr. Fuches at Johns Hopkins did some pioneering research with the drug called Cytoxan, one of the oldest chemo drugs we have, commonly used in transplant, and he found, based on animal models, that if you give miss-matched stem cells that

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should react to the host, that is, I am donating these cells that should recognize that they are in a foreign body and they should want to treat you like a virus, that if you give them some big doses of this cyclophosphamide drug, which is also called Cytoxan, it will kill off the cells that are reactive and what are left are cells that get along. So rather than setting up kind of like a jihad inside your blood, which would otherwise happen and be a total mess, all the old cells and the new cells, even though they do not match, shake hands and agree to live in peace. It is really incredible.

Chagpar Some of us would like to think about that approach in the Middle East, but we will not go there. That sounds pretty good then, so if you are a donor, either you are the sibling of somebody or you are a half matched relative, or you have donated, is that just like taking blood? You do not need to have bone marrow taken from you?

Gore There are different ways of donating stem cells and one of the most common ways is the donors are primed with a growth hormone called GCSF, which is commonly used to help cancer patients, but basically revs up the bone marrow cells so that some of the stem cells actually will circulate in the blood and then the people are hooked up onto what is called an apheresis machine, which is how people donate platelets, and blood is taken out of one arm and put back in the other arm and the stem cells are collected, that is one method. Another method is to take the donor to an operating room and either under general anesthesia or spinal anesthesia actually harvest bone marrow like we do with the large needles and there are pluses and minuses and it is probably more sophisticated than we need to be to determine what is best, but those are the different ways to donate, but either way the donor, even if you go to the OR and have a bone marrow harvest, most of those people who are runners or whatever are back on the road within a few days with a little bit of Tylenol.

Chagpar And most of the time do you find that donors are pretty happy to donate?

Gore They are, and it is one of the best experiences people can have because they are really doing their best to save a life, whether it is a loved one or even an unrelated donor from across the world. I often have patients that say, my third cousin wants to be a donor for me as well. The chance of a third cousin being a match for that person is almost zero, but I say, what your third cousin should do is go on the registry because there is somebody in California whose third cousin wants to donate for them and that California person's cousin may be the direct match for you, and your cousin may be the match for somebody in Germany, and it is like a whole network of human love and people giving to each other. It is really a beautiful thing and it is quite moving, but people need to be on the registry for it to work.

Chagpar You mentioned initially that the patients need to be prepped for this infusion with chemotherapy and radiation therapy and it sounds like that would make you feel a whole lot worse before you feel better. Tell us more about how that works?

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Gore Well there are two different kinds and it is very complicated. There is what used to be called a full transplant, and that is where basically we take an atomic bomb full of chemo, or chemo and radiation, and wipe out the marrow. That is called myeloablative. Myelo- again means marrow, -ablate means fry. We are frying the patient's stem cells and if we do not give them a source of stem cells through a transplant, their bone marrow is never going to make cells again and they will have a condition we call aplastic anemia where they just cannot make any cells, so that is the full transplant and that is still used often in younger patients under certain circumstances but over the past several years what has become increasingly interesting is something called areduced intensity transplant, or non-myeloablative where we do not fry the bone marrow. It is a much lighter treatment. As a matter of fact, at some places like Johns Hopkins it could be done even as an outpatient and we hope to bring outpatient transplants to Smilow in the next couple of years as well, and in the nonablative transplants, if you never got a source of stem cells, your bone marrow will recover. So it is not like we are giving you lethal treatment. You would still have your disease unfortunately, but in the nonablative transplants or reduced intensity, you get the stem cells, they are able to get ahold and remarkably they kind of outdistance your own cells so they can take over and the idea is that these new cells will see any bad guys that are left behind, any leukemia, stem cells, any myelodysplastic syndrome stem cells, any lymphoma stem cells and gobble them up like Pac-Man. So it is not just a chemo treatment, it is really having somebody else's marrow or stem cells be guided missiles to recognize your bad guys as bad guys and cure you by killing off those stem cells.

Chagpar Oftentimes when we talk about organ transplants, we talk about patients being on immunosuppressive therapy forever.

Gore Right.

Chagpar So that their cells do not reject this new organ that they got, but in stem cell transplant it seems like that might not be the case. Tell us more about that.

Gore In fact, it is the opposite, because the new cells have taken over, you have now a new immune system, which may not recognize the body it is in as being the right body, especially if it is a mismatch. So they may decide your liver would make a tasty lunch or your skin might be a tasty meal and that is called graft-versus-host disease. So the cells given to you are called the graft and you as the patient are the host and that is a very serious situation from which patients occasionally die and it used to be a major cause of death, but again some of the newer approaches, for instance, this post transplant infusion of cyclophosphamide that my colleague Dr. Fuches developed has pretty much gotten rid of the most serious graft-versus-host disease, so we need a little bit of immunosuppressive therapy during the first month or so after transplant to get everybody to get along really well, but over the course of six months that is usually withdrawn and unless

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somebody develops serious graft-versus-host disease, which does require treatment with immunosuppressive drugs, sometimes just prednisone and steroids and sometimes other serious drugs, the patients will not be on immunosuppressive therapy after three to six months and like I said, they will be living a normal life after the first year usually.

Chagpar So if you can get through that transplant and the first three to six months where you take some drugs to make sure that everybody gets along, then you are all better and then you never need to worry about this disease coming back?

Gore Well no unfortunately, I wish that it were that simple because even a successful transplant does not guarantee a cure. Particularly in my disease, myelodysplastic syndrome, and the one that I treat most, even in the best of cases, only about 40% of the patients who get transplanted are cured and that means that let's say 15% we talked about are going to die, 40% are cured. That means 45% of the patients made it through the transplant fine, but they relapse, their disease recurs. Fortunately, we have treatments for those patients too. So all is not lost, obviously we are all disappointed, the patients are disappointed, the donors are disappointed, and I am disappointed, but all is not lost because we have treatments that can still be delivered with curative intent and try to rescue those patients as well.

Chagpar In our last 30 seconds, give us a snapshot of where you think the future is in hematologic malignancies.

Gore We are studying people's mutations, we are getting more specific drugs, we are individualizing therapy and we are developing treatments that have more and more curative intent and we hope to be continuing to increase the number of people who are cured through the use of clinical trials.

Dr. Steven Gore is the Director of Hematologic Malignancies at Smilow Cancer Hospital. If you have questions or comments, we invite you to visit yalecancercenter.org where you can also get the podcast and find written transcripts of previously broadcast episodes. You are listening to the WNPR Connecticut Public Media Source for News and Ideas.