Clinical Trials for Hematological Malignancies

Guest Expert:
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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. Dr. Chagpar is Associate Professor of Surgical Oncology and 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, Dr. Chagpar is joined by Dr. Steven Gore. Dr. Gore is the new Director of Hematologic Malignancies at Smilow Cancer Hospital. Here is Anees Chagpar.

Chagpar Let’s start by talking about what exactly a hematologic malignancy is?

Gore A hematologic malignancy refers to any cancer that affects the blood and lymphatic system, so this includes cancers of the blood, bone marrow and lymphatic systems such as leukemias, lymphomas, multiple myelomas, and so on.

Chagpar I think a lot of people have heard about other kinds of cancers, breast cancer, lung cancer or colon cancer sometimes going to lymph nodes, but this sounds like it is something different.

Gore Exactly, it is a common confusion. These are tumors which derive from what we call stem cells or grandparent cells that would like to turn into normal blood cells or antibody forming cells or infection fighting cells, but because they are malignant they increase in number and take over important spaces that the real blood cells should be taking over. In contrast, when you have a metastatic solid tumor like breast cancer, these are cells that have escaped from the tumor and set up shop in a lymph node and then the lymph node grows, here if you have a lymphoma you have got a stem cell that would like to turn into a lymphocyte which usually makes antibodies or fights infection, instead it grows and makes tumor in a lymph node.

Chagpar So they are like tumors that start in the lymph nodes or start in the blood as opposed to starting somewhere else?

Gore Exactly.

Chagpar You mentioned a few different kinds of cancers that fall under this big umbrella of hematologic malignancies, lymphomas, and leukemias, what are the differences?

Gore It is a good question and they all certainly overlap. Traditionally leukemias refer to cancers where the primary sign that led to a diagnosis was an abnormality in blood counts and most classically an elevated blood count, -emia usually refers to too much of something in the blood, and -leuk refers to white cells so leukemia really means elevated white blood cells in the blood, but that is just a historical designation because in many leukemias in fact the blood counts are too low, but in general leukemias have to do with things that manifest primarily in the blood, in contrast to lymphomas that effect cells that would like to turn into lymphocytes if they had not become stupid.
cancer cells, and lymphocytes again make antibodies or fight infections or fight cancer. People have heard of B cells and T cells, T cells are results which are often deficient in HIV patients so people are often more familiar with T cell counts. So B cells and T cells are lymphocytes and in lymphomas these are tumors of B cells or T cells or related cells, cells which cannot become one just yet, but would like to be. There is overlap, so there is a disease called chronic lymphocytic leukemia, for example, which is considered to be a leukemia but it is really a low grade lymphoma because the cells are really lymphocytes.

Chagpar And you mentioned another malignancy that falls under this big umbrella. Tell us about that.

Gore For multiple myeloma, some people call this a bone cancer because unlike these other malignancies this tumor is a tumor of cells called plasma cells and plasma cells are the antibody forming cell so when the lymphocyte matures, it turns into plasma cells which are a factory for manufacturing immunoglobulin, or antibodies, and in multiple myeloma you have got malignant cells that when it grows up it turns into plasma cells. It is a malignant stem cell that turns into a plasma cell and forms tumors of these plasma cells in the bone, which unfortunately eats away the bony part of the bone so you often get holes essentially, holes filled with tumor cells in the bone and the most famous person recently who is well known for her battle with multiple myeloma was Geraldine Ferraro, she I think brought multiple myeloma national attention.

Chagpar Is it fair to say that multiple myeloma, which affects mature B cells or plasma cells, is a type of lymphoma if a lymphoma could be of B cells?

Gore Yes, absolutely. I think that many of us like to classify the heme malignancies into two major categories, one would be the category of tumors, which derive from these lymphocytes and we would call those lymphoid malignancies, or lymphoid cancers, and the other category is those tumors that are of cells that would like to become any of the other blood cells and we lump that group of blood cell into something myeloid cells, which really just means bone marrow, myeloid really means bone marrow, and those are myeloid malignancies and then it does not really matter so much if they are growing as tumors in the lymph nodes or as mostly high counts in the blood in the bone marrow, we can say it is a myeloid malignancy or lymphoid malignancy and we do not have to care so much about whether we call it a leukemia or a lymphoma, but that is very confusing to many patients because as doctors we often use these terms interchangeably because we know better and I might say, well your lymphoma, and they say I thought I had leukemia and I have to go back and say, “Yes you have a lymphoid leukemia" that we also consider to be a lymphoma and it is important for patients I think to not get too hung up on the nomenclature and really focus with their doctors on what it means for them. What can I expect? How are you going to treat me? What is my life expectancy? What can I expect my quality of life to be and where do I get information about this? What organization should I go to for patient advocacy to get information?

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Let’s talk about all of those things. I think that is a really great place to start and I think our listeners will be very interested in that. But the first question that I always like to start with is, how do they present?

Probably the most common set of symptoms for most of these diseases are what we call constitutional symptoms, and those are generalized symptoms, say fatigue or sometimes low grade fevers, just dragging and not feeling right. So say a 48 year old has three teenagers and is schlepping all around but used to be able to run a mile every once in a while and they just cannot do that, or the executive who is used to being on his treadmill and he cannot do what he usually can and sometimes it is very subtle, sometimes it is dramatic with multiple myeloma because you have got these lesions in the bone, there can be pain or people can present with a fracture because this thing has been growing in one of their long bones and is weakening the bone and some small event happens and they present with what we consider a pathologic fracture. So those are the main things and some of the lymphomas people are more familiar with, Hodgkin’s disease which is a kind of lymphoma that is very well known, but lymphomas will often present with a lump, an enlarged lymph node and I think people are used to showing lymph nodes to their doctors and say, should I be worried about this and often if they have had a sore throat or something the doctor usually appropriately is not very concerned and says, let’s keep an eye on it for a couple of weeks and if it does not go away or is getting bigger, then we might need to do a biopsy.

While you were describing some of those symptoms I was thinking, Steve, maybe I should come and see you, but let’s say you are 40 something and you have been kind of dragging and tired and you are not feeling yourself. How do you know whether this is just you are having a bad day because this is called life, or if it is something to be worried about? How do we go about figuring that out?

That is a challenge and I really think it indicates why it is very useful for people as they approach middle age in particular, to have a primary health care provider with whom they have a good relationship and who has seen them on a regular well-patient health maintenance platform and when the patient is starting to think they are not sure, they feel like they are sliding, they can go to them. There are many things that cause fatigue, I do not want your listeners to think "Oh my gosh, I have been tired for two months, I must have leukemia." I mean there are much more common things like low thyroid level that are infinitely more common. People need to get checked. I think the thing to do is if you think things aren’t going and people have a cold and I think people can take Tylenol for a couple of days, but if things are really staying significantly different in terms of quality of life and energy, they probably need to see their primary care physician and a routine physical exam would be the first thing and the doctor may identify something very simple or to reassure they may want to do some blood test including thyroid function and make sure you are not becoming diabetic, if you have any symptoms suggestive of that. Then if there are persistent
symptoms, a complete blood count is often done, which if there is anything wrong in the blood and bone marrow that is usually a pretty sensitive indicator that the further investigation should be looked and of course the physical exam should reveal any areas of enlarged lymph nodes or enlarged spleen if that is happening.

Chagpar  Let’s suppose you go to the doctor, you have these symptoms, they do a complete blood count and they find that your blood cells are really low or really high and they are worried about a hematologic malignancy, what often is the next step?

Gore  Those are different scenarios, but when the blood counts are high the next step is to have an expert look at the blood cells and that often happens in the hematology laboratory because heme lab tests are usually highly training to recognize the different types of cells and see whether these are mature cells, normal blood cells, which doesn’t mean the patient isn’t sick but it puts in a different category then if they are very immature cells if they are very very immature cells then that person potentially may have what we call an acute leukemia and that is often treated as a medical emergency so that patient will either have urgent referral to an oncologist with expertise in hematologic malignancies, or might be directly admitted depending on how high the white count is. If the counts are low then it is more of a gradual workup as an outpatient and it depends on whether the white count is low by itself, whether the patient has a low red count which we call anemia, whether the blood platelets which are the clot forming cells are low, or some combination of the three and there are different evaluations for all of them, and I think we get most concerned when all three are low. Peoples are certainly familiar with iron deficiency, anemia, and that is the most common cause of anemia especially in menstruating woman, so it really depends on the exact abnormalities the doctor finds but will always need to increase tests or additional tests.

Chagpar  We are going to pick up on what happens after all of these tests are done when people are found to have hematologic malignancies and talk more about treatment and prognosis when we come back after we take a break for a medical minute. So please stay tuned to learn more information about hematologic malignancies with our guest Dr. Steven Gore.

Medical Minute  This year over 200,000 Americans will be diagnosed with lung cancer and in Connecticut alone there will be over 2,000 new cases. More than 85% of lung cancer diagnoses are related to smoking and quitting, even after decades of use, can significantly reduce your risk of developing lung cancer. Each day patients with lung cancer are surviving, thanks to increased access to advanced therapies and specialized care, new treatment options and surgical technique are giving lung cancer survivors more hope than they ever had before. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new

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treatments for lung cancer. An option for lung cancer patients in need of surgery is a video-assisted thoracoscopic surgery also known as VATS procedure, which is a minimally invasive technique. This has been a medical minute. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

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 talking about hematologic malignancies and right before the break we were talking about how so many of these different types of blood and lymphatic cancers present oftentimes with subtle symptoms and we were talking about how these patients get worked up with blood tests, some of which require an immediate referral to a hematologist. Dr. Gore, take this from there, what are the most common reasons why a patient would be referred to see you?

Gore Usually there is a doctor who has identified a problem with abnormal blood counts and because I am a tertiary kind of referral doctor the patient usually sees a hematologist or an oncologist with heme expertise who does a bone marrow test. And a bone marrow test usually is done in the hip bone, but sometimes the sternum is numbed up very thoroughly and the skin of course is first numbed and a needle is actually put into the bone to suck out some bone marrow and then a slightly larger needle is used to core out a little piece of the bone for the pathologist to look at. I have had one and they are tests that have terrible reputations and they are slightly uncomfortable but nothing that one cannot get through.

Chagpar So you have somebody take this needle and then a larger needle and put it into your bone, and then what?

Gore Those are processed by ahematopathologist, pathologists specializing in hematology, and we usually have some information right away because the smear is made of the cells which are sucked through the needle and you can often get information pretty quickly about whether there is a problem and then that problem is characterized by the pathologist and often specialized tests are sent on the bone marrow cells to get further more detailed biological tests that ultimately will help us understand the most appropriate longterm strategy for that patient and prognostic information.

Chagpar So they do this bone marrow test and they find some abnormalities, will the bone marrow test help them to figure out which type of cancer this is in the whole spectrum of hematologic malignancies?

Gore Absolutely, it is much like if you have a lump in your breast, you are sent to a surgeon or an interventional radiologist who does a biopsy of that breast tumor and now we know that there are many kinds of breast cancer and specialized tests are done to identify whether it is breast cancer and what subtype that might indicate different kinds of treatment, whether you might use hormone
treatments or chemo treatments. Similarly, the bone marrow aspirant and biopsy hopefully will yield a very specific diagnosis and we are getting better and better at looking at chromosome abnormalities and gene mutations and other abnormalities that can really help us into a whole new range of patient specific treatment. That is really the future, but certainly we can give a specific diagnosis and usually we get the results of the bone marrow test the same day.

Chagpar Dr. Gore, I know that you recently came from Johns Hopkins and as we were talking about before the break, with all of these hematologic malignancies it seems to be a rather a large umbrella. Is there a specific type that you are specialized in or do you kind of treat all types of hematologic malignancies, how does that work?

Gore My research expertise and interest has been in a specific kind of myeloid malignancy called myelodysplastic syndrome and in the old days this used to be called preleukemia because it did not have high white counts that we talked about but now we have recognized it as what we would call a chronic leukemia. We know that it is cancer because all of the cells are related to each other. They all come from the same stem cell, but because it is a chronic malignancy the cells are still doing the best that they can to try to turn into mature cells, now they are not very successful in myelodysplastic syndrome. Myelodysplastic syndrome really translates as funny looking bone marrow. So these very abnormally maturing cells recognize somehow that they are not really good for anything and they kill themselves off in the bone marrow and so people end up with very low blood counts and people may be familiar with this disease now-a-days because it is what Robin Roberts is being treated for and she is a well-known TV personality who has myelodysplastic syndrome.

Chagpar Tell us a little bit more about how that presents, does that still present with this generalized fatigue, just not feeling myself, I go and get a blood test and bone marrow?

Gore Absolutely, now in the earliest cases, sometimes we find blood counts that are abnormal, which lead to a diagnosis of myelodysplastic syndrome even on a regular health maintenance kind of exam where a CBC is sent, whether it is indicated or not, and you find "Hmm..your blood counts Ms. Smith are all a little low and looking back for the last five years there is a little bit of anemia that really hasn’t been enough to look at and your platelet count has been kind of iffy, and now I am looking at the picture overtime and everything has been drifting down over the last five years.

Chagpar When a lot of people think about cancer though they think about it as being a really serious acute problem, but when you paint the picture of myelodysplastic syndrome it sounds like it is kind of chronic, nobody really had any dramatic event that happened. Is it still a cancer, is it still treated in that way?

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Absolutely, like most cancers, there is a broad spectrum of myelodysplasia. There is some very low grade or what we call indolent myelodysplastic syndrome that may never need treatment, that is the minority, most myelodysplastic syndromes are progressive unfortunately and as they progress the ability of the cells to continue to mature decreases, so you end up with more and more really stupid immature cells. They are called blast cells but we could call them Steve cells or Joe cells, that is just the name of the most immature cell in the bone marrow and as the blast cells pile up we have another confusing thing for patients, which is that over the years the pathologists and hematologists have always picked some arbitrary point where if there were more blasts than a certain percent they were not going to call it myelodysplastic syndrome anymore, they were going to call it acute leukemia and I think this is really unfortunate because biologically your body does not know if you have 5% blasts cells in your bone marrow or 10% blast cells or 30%, it really has to do with how it is impacting your health but nonetheless arbitrarily we have focused recently on 20%, if your bone marrow has 20% blast cells the pathologist are going to change the name from MDS to acute leukemia, and I have advocated across the nation, and people are thinking, here he goes again, that this should be called VVVBMDS, Very Very Very Bad MDS, but the point is that unfortunately people do get sicker and left untreated, people do die of myelodysplastic syndrome so it is quite a serious illness.

And so when people get sicker, what are symptoms that they get?

They become transfusion dependent in order to have enough red blood cells to carry oxygen. They will need red blood cell transfusions or treatment to help them make more red blood cells, we can talk about them. They may be prone to recurrent infections because there infection fighting white cell that are called neutrophils are quite low, and there may have bleeding problems because their blood platelets may be very low or even if they are not low they may not function normally so, even if they have a very good platelet count there may be bruising all over and sometimes that in fact is how patients present because they have unusual bruising.

So you have patients that have had low counts and they are getting worse and they come to you and this is a form of cancer, how is it treated?

That, probably even more than many other cancer, has to be very patient individualized. We look at the bone marrow, we characterize the patient’s prognosis based on a number of clinical prognostic scales that take into account the blood counts, they take into account how many blasts there are, the stupid cells in the marrow, they take into account whether we detect any abnormal chromosomes in the bone marrow, whether the patient needs transfusions and now increasingly whether there are certain gene mutations and that will put people into what we consider a lower risk category or a high risk category and in the lower risk categories we are not aiming necessarily to change the natural course of the disease, because the therapies we have that are effective for the low risk MDS, we do not know if they improve survival or not, they may, we do not know, but we do have therapies which can help quality of life and restore quality of life to even normal by
improving the red blood cell count, improving the platelet counts. So, that is our goal in low grade MDS, we want to try to improve quality of life and try to slow down the progression to worse MDS. Now in high risk MDS, we really need to work to improve survival because if left untreated these patients survival will be limited and ultimately we would like to cure patients and, unfortunately or fortunately, cure for patient with myelodysplastic syndrome in most cases would require a stem cell transplant.

Chagpar Let’s say we have got somebody who has very bad MDS.

Gore Right.

Chagpar And/or acute leukemia, however people want to call it.

Gore Okay.

Chagpar And they come to you and presumably those are people who are in this high risk category.

Gore Absolutely by definition.

Chagpar What exactly is a stem cell transplant and how does that work?

Gore Before, if I may, let me back track, so for this particular patient I need to explore that patient’s goals in life at that point.

Chagpar Let’s say Steve that they want to live a long time.

Gore Well they always say that, but unfortunately stem cell transplant is not a walk-in the park and we are not talking about transplants where you get your own cells back. Some people are familiar with that, these stem cell transplants where you have a donor, either a related donor or unrelated donor and there is no way that a group of patients can get stem cell transplant without excepting potentially a 15% chance of death, it is treatment related. So, it is serious stuff and it is one thing when we are talking about a 70 or 75 year old about a 15% or 20% mortality versus a certain percent chance of cure, they might have one set of approaches to that when they hear those kinds of numbers and we try to be as specific as we can for that patient’s prognosis, but I am often surprised when patients of my age, which happens to be 56, tell me, Steve, I do not like those numbers. My focus is on quality of life and seeing my daughter get married next year and I am not willing to take a 15% chance risk of death even if that is my only curative possibility. So we really need to explore a patient’s goals in life. Let’s say the patient really does want to be aggressive and wants life with gusto and all that. We need to get the patient in some kind of remission for the transplant to be successful and that usually requires one of several therapies, oftentimes

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treatment with a drug called azacitidine or decitabine, these are drugs which were approved in the early 2000, 2004, and 2005, before which we had no designated drugs approved for myelodysplastic syndrome incredibly, or sometimes they are treated with more aggressive chemotherapies in the hospital like we would do with younger patients with acute leukemias where they have the high white counts that we talked about and then if the treatment is successful and their blast count has been reduced well and hopefully they have been achieved remission where we cannot see the disease in the bone marrow then they are eligible for stem cell transplant.

Dr. Steven Gore is Director of Hematologic Malignancies at Smilow Cancer Hospital. If you have questions or comments, we invite you to visit yalecancercenter.org or 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.