

Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at the Yale Cancer Center. 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. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about myelodysplastic syndromes with Dr. Valeria Santini. Dr. Santini is Associate Professor of Hematology at the University of Florence in Italy. Here is Dr. Steven Gore.

Gore Valeria, I wonder if you could give us a little bit of background about how you became interested in hematology as a student in Italy?

Santini I like to answer your question because it is going back to my choices in life and I chose to be a hematologist because I was fascinated by basic and translational research in the lab and I was also very much interested in being a real doctor and taking care of patients and treating them and curing them.

Gore A real medical doctor.

Santini Medical doctor, yes

Gore We have real PhD doctors in the audience who might take great umbrage to that.

Santini Yes, it is true, but the short form for medical doctor MD is doctor and in Italy when you say doctor, even if we all are and we all have a degree, it is the physician.

Gore A dottore, in Italian

Santini Dottore, yes, so the physician was a career that I liked because I wished to take care of people and at the same time, I wanted to find something that could couple laboratory research and care of patients and then I met this very good teacher of mine who is a professor of hematology, now retired, and he gave excellent lectures mixing biology, clinical data and ethical issues and moral issues that were very interesting and challenging, so I moved to his department and I was working in the lab, and then I became a real hematologist in 1998, so a very long time ago.

Gore As I understand it, medical training in Italy begins earlier than it would in the United States because you do not go to the equivalent of four years of college before medicine, is that right?

Santini Yeah, that is right. We have to make the choice of our life at 18, 19-years-old.

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Gore I could not have done that.

Santini It was very hard for me. I wanted to be an art historian, being raised in Florence. I wanted to be a philosopher. I wanted to be many things and then in the end, I chose what I thought was useful for mankind and when you are a teenager these are issues that are really strong and the feelings are very strong, so I started medical school and medical school lasts six years for us and when you are finished, you have one year of practicing in the hospital and then you have a national exam and then you may practice medicine in general.

Gore And you were 25 years old at that time?

Santini Yes, more or less. I ended up being 24.

Gore You were very accelerated, of course.

Santini I wanted to finish early because then after that you have postgraduate school which takes you five years more to become a hematologist.

Gore I see, is that a clinical training program or book training? Santini It is both, you have to work in the hematology department and then you have to also have theoretic training, quite a lot, so it is a beautiful period in which you are building up your specific interest in hematology and at the same time, you touch up on all the diseases and subjects and you see patients.

Gore But some of your training was done outside of Italy, am I mistaken about that?

Santini No you are right. When I started hematology, I was very interested in acute myeloid leukemia and acute leukemia, so I picked the best place I could go to in Europe at that time which was Erasmus University and in that year it was Daniel den Hoed Cancer Center in Rotterdam in the Netherlands and I was trained and my mentor kept me there for three years and these were the most productive and challenging years in my training.

Gore It must have been hard as an Italian speaker to be functioning in a science lab in Holland. I cannot imagine you learned Dutch in Italy.

Santini Of course not, and Holland was the only country I had never imagined to go in my life. I knew it for tulips and for nice people and kind people, so when I arrived there, it was little bit of a cultural shock, things were a little bit different then, now they are more similar everywhere, but then people were very kind and they all speak English of course. They spoke excellent English, so for me, it was easier and then a little by little, I learned Dutch to be more in touch with them.

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Gore You are probably in a very small minority of Italians who also speak Dutch fluently, I am guessing.

Santini None that I know.

Gore So after the Netherlands, then you returned to Florence?

Santini I came back to Florence to my old department and I started working there as a hematologist and I got my position early in '94.

Gore That is fascinating. I know that you mentioned that while you were in Netherlands you were working on acute leukemia, perhaps you could explain to our audience, because I think now your interest is more in chronic leukemias, could you explain to our audience, I think they think that an acute leukemia patient is probably much sicker, how do we differentiate between different kinds of leukemias?

Santini When I see a patient with leukemia and I have to explain the prognosis, I always say, do not look at your neighbor who has leukemia because every single individual is different. There are hundreds of leukemias, you have myeloid, a certain kind of cells in the bone marrow. You have the lymphoids which are more prone to give you enlargement of lymph nodes or spleen and inside these two types, there are many other subtypes, characterized by different genetic, molecular characteristics by clinical characteristics, so it is very weird to speak about leukemias as a whole. You have to differentiate and the prognosis is very different. You can really only tell patient by patient, not generally, and then I moved from AML and ALL, the short form for acute leukemia to myelodysplastic syndromes which at that stage were thought to be sort of a pre-leukemic state.

Gore What does that mean, preleukemia?

Santini The possibility that a patient with myelodysplastic syndrome developed overt leukemia is not 100%, is not always so high, but some years ago in the beginning of the studies of myelodysplastic syndromes, they were called preleukemia because they were seen as a state preparing to overt leukemia, so an increase in the number of immature cells and then as a result, you had severe anemia, neutropenia, prone to have infections and bleedings, so the disease was seen only as a prodrome to more severe disease.

Gore How would I know if I had a myelodysplastic syndrome, that sounds pretty scary?

Santini It is a severe disease even if it is not a leukemia. You have low counts, very low counts.

Gore Blood counts, low blood counts.

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Santini Low blood counts, and you have it usually when you are in your mature age, 60 or more, the mean age in the western countries is 70, so more or less,

we say elderly, but now a 70-year-old is no longer elderly.

Gore It is pretty young to me.

Santini Yes, exactly, they are very fit, so these people just by chance or because they feel tired, they discover that they have anemia, so low hemoglobin, they can bleed and they discover they have low platelets and can have recurrent infections and they have low neutrophils which are a kind of white blood cell defending us from bacterial infections and fungal infections. So, all of a sudden you realize that your blood does not work as it used to and your bone marrow which is where your hematopoiesis or blood cells are formed is filled with progenitors trying to mature and not succeeding.

Gore So what happens to those cells that are not turning into good blood cells.

Santini They are dying in the bone marrow mainly, so that is why you do not have anything in your peripheral blood and you have an overcrowded bone marrow.

Gore Wow, that sounds pretty dangerous.

Santini It is, even if you are not transforming to leukemia as I mentioned before, it is a disease that has to be taken seriously and has to be treated early to obtain nice results. We have the possibility to do so, and the most important thing is to be aware that this disease exists.

Gore It seems to me that perhaps awareness has become increased at least in the United States because this very famous television personality, Robin Roberts, has come out publicly, I am not sure if you are familiar with her, but she was on one of our news programs called the Today Show and she turns out to have I believe myelodysplastic syndrome which I think they said was caused by chemotherapy she had received for breast cancer. Does that happen?

Santini Yes. That is quite a common problem that we have with solid tumor cancer survivors. We have many cancer survivors, of course happily, but these people receive chemotherapy and sometimes chemotherapy in specific individuals who are more sensitive to these may cause some modification of the cells of their DNA and then in the long run, may lead to myelodysplasia as a secondary damage of chemotherapy. It is not always like that. It may happen in some individuals, but sometimes, myelodysplastic syndrome just arises as a novel disease.

Gore Out of the blue.

Santini Out of the blue completely and the first question I have from my patients is, why did I get this myelodysplastic syndrome and unfortunately, in the majority of cases, I do not have an answer.

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You can say growing old, it does not really mean anything; you can say, you have been exposed to dyes or toxins.

Gore Chemicals.

Santini Chemicals, whatever, but it is just guessing.

Gore Of course in Italy most people are smokers, or at least many people are smokers.

Santini They used to be. Since something like 10 years ago, we cannot smoke in public restaurants.

Gore Really.

Santini Funny enough, people are really respecting the rules so nobody is smoking, and I think this may have lowered the number of smokers, not so much, unfortunately, many young people are still smokers, heavy smokers.

Gore And does smoking contribute to the formation of this disease?

Santini Absolutely.

Gore But hopefully not coffee.

Santini I hope not, especially I hope not espressos.

Gore We are going to need to take a break for a medical minute. Please stay tuned to Yale Cancer Center Answers to learn about myelodysplastic syndrome and the practice of hematology in Italy with Valeria Santini.

Medical Minute It is estimated that over 200,000 men in the United States will be diagnosed with prostate cancer this year with almost 3000 of these diagnoses here in Connecticut; one in six American men will develop prostate cancer in the course of his lifetime. Major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from this disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical exam and a blood test. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to test innovative new treatments for prostate cancer. The Artemis Machine is a new technology being used at Smilow that enables targeted biopsies to be performed as opposed to removing multiple cores from the prostate for examination which may not be necessary. This has been a medical minute brought to you as a public service by Yale Cancer

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Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to WNPR, Connecticut's public media source for news and ideas.

Gore Welcome back to Yale Cancer Center Answers. This is Dr. Steven Gore and I am joined tonight by my colleague, Valeria Santini, who is an Associate Professor of Hematology from the University of Florence in Italy. We are talking about her area of expertise which is myelodysplastic syndrome, a kind of leukemia or leukemia related disorder. Valeria, before the break, we were talking about things which may cause myelodysplastic syndrome or at least that patients want to know what is causing the myelodysplastic syndrome. Have things changed in this disease? You started practicing in the 90s, so about 20 years later, and you are still very young in your field, but over these 20 years, has there been much in the management of these patients or the diagnosis?

Santini There have been major changes, I am very happy to say. The diagnosis is much earlier and is much more precise than it used to be and the most important thing is that together with better diagnosis we have treatments, we have active treatments that were not available 10 years ago. So the patients who got the diagnosis of MDS, myelodysplastic syndrome, were treated only with transfusion as the best supportive care, antibiotics for events as I just indicated.

Gore Infections.

Santini Infections and bleedings and so on and so forth. Now, we have a lot of options that we can offer to these patients for being treated, not cured, unless they are eligible for a transplant.

Gore A stem cell transplant.

Santini Stem cell transplant, hematopoietic stem cell transplant that is possible mainly for patients who are fit and not so elderly, but this is the curative approach still, but the treatment is possible and improvements are really massive with the right treatment.

Gore You mentioned that for leukemias in general, there seemed to be a lot of differences or heterogeneity between the patients. Is this true for this disease as well, myelodysplastic syndrome? Are there many kinds or is it one size fits all basically, one kind of disease.

Santini This is very important to say that there are many myelodysplastic syndromes. Syndromes mean that it is a bunch of symptoms that look the same but does not mean that it is one disease, and we are now aware that there are more diseases called myelodysplastic syndromes characterized by specific genetic lesions or specific features of immaturity in the hematopoietic cells and the bone marrow cells. So you can call them different names, but this is not only a matter of different

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definitions, it is a matter of different prognosis, different clinical characteristics, and therefore different outcomes. You have to pick out specific therapies

for different subtypes and it is very important that the patient is diagnosed precisely.

Gore It would seem that it would be important for patients with this disorder to be seen by somebody who has some special expertise in this group of diseases, at least for a second opinion as opposed to a general oncologist or hematologist?

Santini Surely, they have to be addressed to a specific doctor who has great experience in this disease, because it is very difficult to make a precise diagnosis, to have a good classification and therefore, to have successful treatment.

Gore Do you tailor the treatments based on the patient's underlying biological features or clinical features?

Santini We can do something like that, not completely now but we are on the way to being able to do it more and more and I think in a few years, we will be able to tailor it patient by patient on the basis of biology and of course on the basis of the individual status of the patient. We can do it now at least in one myelodysplastic syndrome that is quite typical and is characterized by the deletion, meaning the loss, of part of chromosome 5. This specific myelodysplastic syndrome is an anemia that is observed mainly in women but not only, and the fact that they carry this genetic chromosome abnormality gives the patient a specific sensitivity to lenalidomide.

Gore What is lenalidomide?

Santini Lenalidomide is a difficult name to pronounce, but it is a very potent drug that just by serendipity was discovered to be very effective in del 5q, in this kind of subtype of myelodysplastic syndrome.

Gore Is it given like chemo in the clinic through the veins?

Santini No it is an oral drug, it is a tablet.

Gore You are kidding.

Santini It is a tablet, but you should be aware that you cannot give it as an aspirin or something like that.

Gore No.

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Santini It is a drug that has to be handled by experts.

Gore It is more expensive than aspirin also, I would imagine?

Santini It is a little bit more expensive. Yes, it is extremely expensive still. We hope that in the future it will be less so, and it is giving a very high percentage of success. It is a very good drug for these kinds of patients who are no longer anemic when they take the drug.

Gore Really.

Santini Yes, they get rid of the transfusions. They get rid of the symptoms of anemia, but when they take this drug they have to take care that the other blood counts are not going down. They have to take care of adverse events, manageable, but you have to know which they are and treat them early and so you can really go back to a very good quality of life, so this is the example of one new therapy that we are using for a specific biological featured MDS.

Gore I know that you led an international study, or at least participated in the international study, that looked at the impact of this particular drug in MDS patients who did not have that chromosome abnormality, is that right?

Santini Yes, it is because usually anemic patients without this chromosomal abnormality respond very well to erythropoietic stimulating factors.

Gore Erythropoietic stimulating factors, that is a very complicated set of words. What does that mean?

Santini These are hormones.

Gore Okay.

Santini These are hormones as insulin or other hormones but the difference is that they stimulate red cells. So if you are anemic and you stimulate your red cells, then you are no longer anemic and you can do this therapy. You can prescribe it for anemic patients. They do respond in a high percentage of cases provided they are not del 5q. They do not have the chromosomal abnormality that I just mentioned. These ones will respond for a short while and then they need the drug which I just talked about and the patients who fail this stimulation with hormones, they are anemic, they need transfusions and what we are looking for is some drug that can avoid transfusion, so we tried to study whether lenalidomide, which is so effective for del 5q, is effective for the others.

Gore What did you find?

Santini We actually found there is a larger proportion of patients, around 26% of patients who do respond to this treatment, but we do not know why, and this is the most important thing because you have

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to select this 25%-26% and on the basis of characteristics, treat them immediately with the drug, but the rest is not responding, and therefore we are working hard to find other drugs that may unblock this situation and restore transfusion independence, so they do not need to go to the hospital, they do not need to sit there for hours and get their transfusion, although I must say that transfusions are saving lives, so you need them, you cannot just say, "I do not want to do it and they are boring," well the patients get really bored and tired, so you need a caregiver, you need to go to the hospital to spend time there and these patients are elderly usually, so they do not like it.

Gore Do you have samples from the patients from your study that may be able to help you learn how to select the patients that will respond to this drug? Is that part of the project?

Santini Yes. We are very busy trying to find a clue as to why they do respond in terms of studying their mutations, meaning problems in DNA, or in their genetic asset and then try to see whether other clinical clues are helping us, but we are still in deep water, I am afraid.

Gore As is often the case. Several times you have mentioned genetic abnormalities in the patient's cells, are these diseases that people are inheriting genetically from their parents?

Santini No, and that is a good point to stress and that is a question I constantly have from grandparents, from my patients who are grandparents and they are very worried that they can pass it on. It is not a disease that you pass on. There is absolutely no danger in this sense. The problems you get, the genetic problems and the genetic abnormalities, are acquired during life and they do not effect the progeny, so the grandchildren are safe.

Gore Good. I think that is common, we have a lot of people on our show talking about genetic abnormalities and I think it causes a lot of anxiety.

Santini Yes, I understand.

Gore But, medically we use the term genetic to mean abnormalities in DNA whether we inherit them or they are acquired, so thanks for helping to clarify that. Valeria, I know that you have spent some time at some US hospitals, and I know you spent some months at MD Anderson Cancer Center in Houston.

Santini Yes, I did.

Gore You visited many places, how do you think things compare in hematology in the system in Italy compared to what you have seen here? I realize you are not an expert in how things are in the United States, but what are some similarities or differences?

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Santini Well, when I was in the States, I was visiting and I was not able to take care of patients first hand, so I just observed and MD Anderson is a specific reality. It is very different from everywhere else I think.

Gore Sure.

Santini They have a lot of new drugs, experimental drugs, and the main vocation of the center is to give new therapies for any disease, so they have a complete different approach from the routine we have and that is one point, so what is very different from Europe is the fact that in Europe we are organized in a way that you are treating your patients without so much support of physician assistants, nurses. There are very few research nurses for instance and nurses

have a marginal role in the management of patients. We are trying to change it to improve the care of the patients but still it is organized in a different way. In the States you have more outpatients that are taken care of than we can do. What we are trying presently to do both in France and in Italy is to have treatment care for patients with MDS on the territory, so we are trying to organize a system in which the nurse during treatment can go and see the patient's at home. Which is by the way very difficult because of the expenses.

Gore Yes, of course.

Santini And the crisis and the budgets are limiting us in this moment. And then the differences between the States and Europe, I would say generally, is the fact that in Europe overall we have a National Health System that is taking care of all the patients, so they all come to you, very rarely you are treated privately, especially not if you are an MDS patient.

Gore And patients do not have to pay for their care, is that right?

Santini Absolutely, nothing.

Gore That is a huge difference and I wish we had more time to talk about that. I realize that you are not a health economist, but it certainly is a difference I have seen in terms of the financial burden to the patients.

Santini Yeah, we have limitations only in terms of general budget but not individually. All the patients are treated with the best drugs that we can get and they do not have to pay.

Dr. Valeria Santini is Associate Professor of Hematology at the University of Florence in Italy. We invite you to share your questions and comments, you can send them 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 format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.