WEBVTT

00:00.000 --> 00:14.200 Support for Yale Cancer Answers comes from AstraZeneca, a biopharmaceutical business that is pushing the boundaries of science to deliver new cancer medicines. More information at astrazeneca-us.com.

00:14.200 --> 00:48.100 Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. 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 the care of patients with multiple myeloma with Dr. Natalia Neparidze. Dr. Neparidze is an Assistant Professor of Medicine and Medical Oncology at the Yale School of Medicine. Dr. Gore is a Professor of Internal Medicine in Hematology at Yale and Director of Hematologic Malignancies at Yale Cancer Center.

00:48.100 --> 00:57.500 <vGore>When I think about multiple myeloma, I am struck by when you read about it in the newspaper, they often call it bone cancer, is that correct?

00:57.500 --> 01:36.900 <vNeparidze>It is a disease of the bone marrow, which forms all of the precursor blood cells and myeloma is a disease that comes out of these forms of white blood cells called plasma cells. Plasma cells grow gradually and overgrow in the bone marrow leading to gradual bone loss and ultimately leading to these thinned bone lesions called lytic lesions and they can produce this abnormal protein called M-protein or monoclonal protein, which then circulates in the bloodstream and can be toxic to the kidneys and other organs. So, it is a disease of a bone marrow and blood.

01:36.900 --> 01:47.500 <vGore>So, the only part that is really about the bone is that it seems to have this effect on thinning the bone and causing problems with the bone as one aspect of its manifestation.

01:47.500 --> 02:00.200 <vNeparidze>That is correct. That is one aspect. In the majority of cases, myeloma is confined to the bones and bone marrow, but there are cases when myeloma cells come out of the bone marrow and infiltrate soft tissues and other organs.

02:00.200 --> 02:13.300 <vGore> And so, that is different than a bone cancer like we remember when Ted Kennedy Jr. when he was a kid had what they called osteosarcoma, that is really a cancer of bone cells, right?

02:13.300 --> 02:21.500 <vNeparidze>That is correct. This is a blood or hematopoietic malignancy which comes out of a type of white blood cells, plasma cells.

02:21.500 --> 02:49.800 <vGore> Gotcha. And when I was coming up in my training, multiple myeloma had really a very grim prognosis. Uually when people were diagnosed, they often had a lot of problems like kidney failures, you

mentioned these fractures in the bones and other problems, and as I recall, their average survival was something like 3 years, which was pretty grim.

02:49.800 --> 03:04.100 <vNeparidze>That's correct. Even as recently as 15-20 years ago, the majority of patients only survived for 3-5 years. And with the advent of all of the newer therapies, the survival has been extended to at least 10 years and much longer.

03:04.100 --> 03:07.500 <vGore>Wow. How does that happen, can you walk us through the changes.

03:07.500 --> 03:22.100 <vNeparidze>There has been really tremendous progress and truly revolutionary changes in the treatment of myeloma over the course of the past 10-15 years. I think the first step was really the development of immunomodulatory molecules.

03:22.100 --> 03:26.700 <vGore> Oh! that is a lot of syllables.

03:26.700 --> 03:48.800 <vNeparidze>These are type of immune therapy or immune modulating agents that boost the immune system by producing certain types of immune cells to fight the multiple myeloma, and the first line of these agents were really thalidomide, lenalidomide, pomalidomide. These are effective agents that are used as the cornerstones of myeloma therapy.

03:48.800 --> 03:54.400 <vGore>Thalidomide, the notorious drug that caused congenital deformities in the 60s right?

03:54.400 --> 04:17.000 <vNeparidze>That's correct. There is this tragic saga associated with it. But later on, it was found to be effective in multiple myeloma through the variety of these immune mechanisms that maybe by targeting certain vessels as well, which modulates bone marrow environment such that it is able to fight multiple myeloma clone.

04:17.000 --> 04:23.300 <vGore>Cool. So, you have got this thalidomie and these 2 other drugs that are similar but newer.

04:23.300 --> 06:13.200 <vNeparidze>Correct, although they have been around and approved for clinical use for over the past 10 years and longer, some of them. And then, the next breakthrough was the development of proteasome inhibitors, which some are oral and others are injectable type of treatment that also modulate type of protein environment within the myeloma cell so that it leads to the killing of myeloma cells. And the first of these agents was bortezomib also known as Velcade and that was the cornerstone of therapy over the past 10-15 years now. It is likely going to be replaced gradually by other more potent agents and these are for instance carfilzomib and other drugs that are working in a similar way. And the next great progress and truly a breakthrough was in 2015 which really was a remarkable year for myeloma treatment, led to the approval of 3 new drugs out of which were 2 were immune-targeted monoclonal antibodies. So, these are antibody large protein molecules that are targeting certain surface receptors on the myeloma cell and these were the so-called daratumumab, which

targets a specific receptor on the myeloma cell and another one called itolizumab, which is also a targeted agent binding to myeloma cells and other immune cells within bone marrow. And that same year, there was also an approval granted to this agent orally available called panobinostat, which also modulates protein environment of the myeloma cell.

06:13.200 --> 06:31.100 <vGore> Well, that is a lot of changes in a very short period of time compared to some of the cancers that I treat, some of which did not have a new drug for about 20 years until recently. So, wow, it sounds like you got so many drugs, so now you do not have to use chemotherapy drugs anymore right?

06:31.100 --> 06:55.000 <vNeparidze>So, we use less and less of the old-fashioned chemotherapy, cytotoxic drugs like alkylating agents, the old drugs that some of which are still used but less and less often. For instance, cyclophosphamide is still used in certain cases where we need to attain rapid control of the disease, treat them actively.

06:55.000 --> 06:54.900 <vGore> That is one of the oldest chemotherapy drugs.

06:54.900 --> 07:18.700 <vNeparidze>That is, that is. But truly to this day, with the advent of all of these new targeted agents, we really do not know what is the best ideal first-line treatment for initially diagnosed myeloma patients and what is the best ideal treatment for patients who have a subsequent relapse or recurrent disease when myeloma returns.

07:18.700 --> 07:23.600 <vGore>Well, how common is multiple myeloma. Do you know how many cases per year in the United States or anything like that?

07:23.600 --> 07:57.600 <vNeparidze>It really is a rare cancer from the standpoint of prevalence because it really represents less than 2% of all cancers and out of blood and hematologic malignancies, it represents in the order of 18-20% of all hematologic cancers. And then, each case is unique in its own different signature. So, cannot be treated as one disease, one unified disease but rather subsets of multiple different variants of it.

07:57.600 --> 08:05.000 <vGore> I am going to have you walk me through sort of how you make decisions or how the patient makes decisions about a therapy, but before we get to that, how do patients find out that they have multiple myeloma, how would you know?

08:05.000 --> 08:14.700 <vNeparidze>So, multiple myeloma is uniformly preceded by this precursor state called monoclonal gammopathy of undetermined significance.

08:14.700 --> 08:16.900 <vGore>You guys like a lot of syllables and a lot of words.

08:16.900--> 08:47.400 <vNeparidze>The silent clinical state, which can be ongoing for several years until it becomes clinically manifested. It gradually

accelerates and becomes an early stage myeloma, which we refer to as asymptomatic or the other term used is smoldering multiple myeloma, which to this date by standard of care does not require active treatment, and these states are completely asymptomatic and silent, do not lead to any symptoms.

08:47.400 --> 08:47.600 <vGore> So you might not know you had them.

08:47.600 --> 0:09:09.6 <vNeparidze>You may not know or patients may have vague symptoms like gradual onset of back pain, bone pain, subtle changes in urination or at times, these changes could be picked up through primary care general practitioner routine blood tests such as complete blood counts and electrolyte levels.

0:09:09.6 --> 09:23.800 <vGore> Okay. So, let's say that you have not been particularly sick and your internist did not pick up on the subtle change, when do you find out you have got a problem?

09:23.800 --> 10:12.600 <vNeparidze>Large majority of cases now with the advent of primary care intervention and screening, they do get picked up based on some of the routine blood tests and anemia is detected or kidney impairment is detected or elevated protein level is detected in the form of elevated globulins and this leads to further investigation and referral to a hematologist. But unfortunately, we still see cases where the full-blown myeloma gets presented at a very advanced stage when there is diffuse lesions and areas of bone thinning throughout the bones, in some cases patients even develop terrible fractures involving the vertebral bodies, the spine or the hips and need urgent emergent surgery and treatment in the hospital.

10:12.600 --> 10:16.800 <vGore> Sounds very painful potentially.

10:16.800 --> 10:25.100 <vNeparidze>It is, and pain and particularly bone pain is an unfortunately a large component of suffering for the patients in myeloma.

10:25.100 --> 10:29.500 <vGore>Gotcha. So, better in this case really to find out at an early stage before that happens.

10:29.500 -->10:56.600 <vNeparidze>Absolutely, just like in other diseases in medicine including cardiovascular disease where prevention is really the key to avoid life-threatening events, so too in myeloma there are strategies being developed in order to address myeloma in these early stages, stages of so-called asymptomatic or smoldering disease and more and more research is being conducted so that we can intervene early and prevent organ-related critical complications.

10:56.600 --> 11:05.100 <vGore> So, if somebody has one of these abnormal blood tests, is that sufficient to make a diagnosis of multiple myeloma or are there other tests required?

11:05.100 --> 11:41.300 <vNeparidze>Certainly additional testing is required and these involve certain types of blood tests and urine tests as well as x-rays, but really more and more we are using advanced imaging modalities including either PET scan or a magnetic resonance imaging, MRI and ultimately the

definitive diagnosis is based on the bone marrow aspiration and biopsy and getting the sample of the bone marrow so that a hematopathologist can give us a definitive diagnosis of multiple myeloma.

11:41.300 --> 12:13.800 <vGore> I see. So a patient has gone through all this stuff and hopefully they are still in pretty good shape and they have had their bone marrow test and these MRIs and such and now they come to you or they come to any doctor, let us say they come to their local oncologist, it seems like the local oncologist has now a whole laundry list of drugs that she can use, how does one sort through the morass of options?

12:13.800 --> 13:36.800 <vNeparidze>So, the first question that gets asked at the time of initial diagnostic workup is of course does the disease have actual myeloma defining critical components such as low blood counts or bone lesions or extreme elevation in the proteins called the free light chains and if none of these criteria are met, then patients might have this smoldering or early stage disease called asymptomatic myeloma, and in those cases, I would really urge all of the hematologists and clinicians to consider enrolling them on therapeutic clinical trials because this is the area where care is really not very well defined. There have been couple of studies examining the role of this drug, oral drug called lenolidomide, which prevents progression of disease but ultimately does not improve overall survival. So, the question that gets asked is, do these novel agents including monoclonal protein antibodies and targeted therapies be incorporated in this early stage of disease? So, the asymptomatic or smoldering myeloma is really an area which needs further investigation and standard of care by text book would be observation, but patients and clinicians are really encouraged to offer them participation in clinical trials, many of which are open at Yale Cancer Center.

13:36.800 --> 13:57.200 <vGore>And other cancer centers as well I am sure. Well, this is really fascinating and I am going to want to follow up on what happens to the people who have more than the asymptomatic multiple myeloma, but right now, we are going to take a short break for a medical minute. Please stay tuned to learn more about multiple myeloma with Dr. Natalia Neparidze.

13:57.200 --> 14:14.900 Medical Minute Support for Yale Cancer Answers comes from AstraZeneca, a biopharmaceutical business with a deep-rooted heritage in oncology and a commitment for developing cancer medicines for patients. Learn more at astrazeneca-us.com.

14:14.900 --> 14:59.700 This is a medical minute about head and neck cancer. Although the percentage of oral and head and neck cancer patients in the United States is only about 5% of all diagnosed cancers, there are challenging side effects associated with these types of cancer and their treatment. Clinical trials are currently underway to test innovative new treatments for head and neck cancers and in many cases, less radical surgeries are able to preserve nerves, arteries and muscles in the neck, enabling patients to move, speak, breathe and eat normally after surgery. More information is available at YaleCancerCenter.org. You are

listening to Connecticut Public Radio.

14:59.700 --> 15:47.500 <vGore>Welcome back to Yale Cancer Answers. This is Dr. Steven Gore. I am joined tonight by my guest Dr. Natalia Neparidze and we are discussing the care of patients with multiple myeloma. Natalia, before the break, you were telling me you would walk me through how people get diagnosed with multiple myeloma and that for patients with kind of a low-grade disease or asymptomatic disease as you mentioned, the standard of care would be to just observe the patient but there are clinical trials investigating whether an intervention at that time might help prevent progression of disease or make people live longer. So, what about the patients who have bonafide disease that needs to be actively treated that anybody would agree need to be treated, they still have a lot of drugs to choose from right?

15:47.500 --> 17:32.500 <vNeparidze> Absolutely. And treatment paradigm is continuously changing and evolving for multiple myeloma, especially with the advent of all of these new drugs and targeted agents. So, the old-fashioned standard of care which is still being done would consist of drugs like immunomodulatory drugs that I mentioned before, oral agents like lenolidomide in combination with proteosome inhibitors and combined with steroids, this would be followed by in appropriate by high-dose melphalan and stem cell transplant, which can be considered in certain cases of younger patients and ultimately once the patients achieve remission following this therapy, we would certainly offer them continuation of maintenance therapy, which is the cornerstone in myeloma treatment because ultimately to this day, myeloma is considered not curable and ultimately virtually everybody will develop recurrent or relapsing disease and therefore, continuous treatment with oral maintenance agents is the current standard of care. And because we do not know what is the ideal initial treatment for these patients, again here the emphasis is to consider enrolling patients on clinical studies which may offer treatment with further novel therapies and monoclonal antibodies. In fact, there has been couple of studies that has already been published and we are more and more going to be utilizing these targeted monoclonal protein antibodies like daratumumab in the frontline initial treatment of patients with multiple myeloma.

17:32.500 --> 17:44.500 <vGore> So, you had mentioned that right now you do not consider the disease to be curable, but I thought you said people were getting stem cell transplants, I thought stem cell transplants were curative therapy.

17:44.500 --> 18:05.800 <vNeparidze> Not for multiple myeloma unfortunately. It definitely does extend the duration of remission and it prolongs the progression-free interval, but ultimately with or without the high-dose melphalan and autologous stem cell transplant, both groups with or without transplant live about the same duration. Same longevity.

18:05.800 --> 18:20.100 <vGore>I see. So, they have a longer remission but the disease still comes back. And this is a transplant where people's own cells are given back, not a donor cells is that right?

18:20.100 --> 18:41.100 <vNeparidze>Exactly. So, once the patient gets treated with the initial treatment for a number of few months, this is then followed by filtration of the patient's own autologous stem cells and high-dose melphalan is given as part of the purging to eradicate any residual plasma cells from the body and then infuse their own stem cells back.

18:41.100 --> 18:43.500 <vGore> So, it knocks it down but it does not knock it out.

18:43.500 --> 19:10.800 <vNeparidze>It does not completely eradicate the disease and therefore more novel and more promising immune therapies are needed for that stage of disease, which ultimately likely is going to gradually replace the old-fashioned melphalan and these are going to be likely in the form of newer immunotherapies and cell therapies, which are likely going to advance treatment and potentially make it curable disease.

19:10.800--> 19:14.000 <vGore> Could you tell us something about any of these new therapies.

19:14.000 --> 19:41.600 <vNeparidze>So, there is really a rapid expansion of the field with all these newer agents. On one hand, we have more and more of these protein antibody targeted monoclonal antibodies. On the other hand, we have antibodies that are coupled with the toxic drug that deliver the drug directly to the myeloma cells and target them directly, these are called antibody drug conjugates.

19:41.600 --> 19:45.800 <vGore>So, basically like a missile with a chemotherapy warhead on the surface?

19:45.800 --> 20:38.700 <vNeparidze>Exactly. There is another approach with monoclonal antibodies called bi-specific T-cell engager antibodies which on one hand bind multiple myeloma and on the other hand they engage immune system and boost the person's immunity such that it fights the multiple myeloma clone and ultimately there are these cell therapies which really is entering the field of myeloma earlier and earlier in the course of disease and these are called chimeric antigen receptor T-cells and other types of cell therapies including modified T-cells and generic T-cells, which will be developed out of either a patient's own blood or from a donor's blood and target so that it eradicates multiple myeloma.

20:38.700 --> 20:49.300 <vGore> Well, how can you take a patient's own immune cells which clearly are not fighting the myeloma in the body and engineer them to fight the myeloma, what is involved with that?

20:49.300 --> 21:31.500 <vNeparidze>It involves this procedure called apheresis or leukocyte collection, which collects a person's own lymphoid cells. These lymphoid cells are later modified in the syringe to express certain type of warheads on the surface. In some cases, these cells are genetically modified to express these and once this product of a patient's own T-cells, the modified T-cells is mature and readily available for use, these cells are reinfused into the patient's bloodstream.

21:31.500 --> 21:32.900 <vGore>Like a transfusion?

21:32.900 --> 21:36.600 <vNeparidze>It is similar to transfusion, but a lot more involved.

21:36.600 --> 21:43.900 <vGore> Gotcha. And then, these modified T-cells somehow are able now to recognize and fight the myeloma cells, is that right?

21:43.900 --> 22:04.600 <vNeparidze> Exactly. Because they are targeted against certain relevant targets and receptors on the surface of the multiple myeloma cells, majority of these cases for myeloma, the receptor that is commonly used as a target is something called B-cell maturation antigen or BCMA and others.

22:04.600 --> 22:14.300 <vGore>Gotcha. And how sci-fi is this. I mean, are any of these things going to be primetime anytime soon?

22:14.300 --> 22:35.600 <vNeparidze>This is very much the reality in our current practice. All of these targeted therapies with T-cells therapies are currently investigational and available through therapeutic clinical trials, but I would anticipate that in the coming several years, they may receive approval from FDA and may be utilized for the treatment of myeloma.

22:35.600 --> 23:02.000 <vGore> That is really amazing. It sounds like there is a lot for patients at every stage to think about and consider and probably is a reason to see a myeloma expert at least as a second opinion in helping guide your oncologist unless you see a myeloma specialist.

23:02.000 --> 23:21.200 <vNeparidze>I agree. I think that will be an opportunity for the patient to be able to see a specialist and be able to have access to all of the novel research drugs, which potentially can be life saving and can have durable good influence on their outcomes.

23:21.200--> 23:29.100 <vGore> Now, I understand that your group at Yale has recently made a move away from the downtown campus.

23:29.100 --> 23:45.100 <vNeparidze>That is correct. This is an expanded site of our multiple myeloma program, which allows us to have a lot more space to conduct our clinical care as well as therapeutic clinical trails and research.

23:45.100 --> 23:47.600 <vGore>And so, the new myeloma center for Yale is in North Haven as I understand it?

23:47.600 --> 24:01.500 <vNeparidze>That is correct, in North Haven and it provides easy access to patients location wise as well as a lot bigger space and state-of-the-art technology.

24:01.500 --> 24:11.200 <vGore> Wow! And they can get what they need there and without often having to come downtown if that is convenient for them is that right?

24:11.200 --> 24:11.400 <vNeparidze>Absolutely.

24:11.400 --> 24:13.900 <vGore>Well that is pretty needed, and all of you myeloma doctors are out there?

24:13.900 --> 24:14.200 <vNeparidze>That is true.

24:14.200 --> 24:19.200 <vGore> So, it is like a home away from home for you guys.

24:19.200 --> 24:19.500 <vNeparidze>It is our new domain.

24:19.500 --> 24:50.100 <vGore>Gotcha. I think it must be so fascinating and of course I have witnessed this in my career from a distance, but you have really in your shorter term career as a blood malignancy expert really seen a tremendous evolution of outcomes for your patients.

24:50.100 --> 25:08.000 <vNeparidze>That is correct. So, in 2006, 2007 and 2008, when I was still in training, we were just beginning to utilize the drugs like lenolidomide and bortezomib that had just come to market at that time, and that sounds so old fashioned now already some 15 years later.

25:08.000 --> 25:42.100 <vGore> Well, I can tell you that earlier than that, I was around when bortezumib was being developed as a phase-I drug that is to say just trying to see what levels were toxic and there was concern that it was not going to find the disease for which it was active, it was almost thrown out in studies from the National Cancer Institute before this information about myeloma kind of stuck, so you know, just to give you some perspective from just before your time that drug almost got tossed out.

25:42.100 --> 26:02.100 <vNeparidze> That is quite fascinating. And it shows you how important it is to conduct rigorous clinical trials and pursue the answers through developmental therapeutics and research because this is the only way we define how to best treat our patients and how to improve the care and outcomes.

26:02.100 --> 26:12.700 <vGore>I almost feel like it is not fair that you get to enjoy all these good outcomes without having had to suffer with your patients for years and years of bad outcomes.

26:12.700 --> 26:39.200 <vNeparidze>I think the suffering has changed and it has become different, so now we deal, I think with the advent of the new drugs, there comes a responsibility on the part of physicians for dealing with all of these newer side effects that are emerging and just beginning to be defined, but I think we are becoming more and more educated in how to deal with these and so, in the hands of a specialist, generally these side effects are manageable and can be dealt with.

26:39.200 --> 27:04.900 <vGore> Now, I know that when I see some of the myeloma patients when I am providing inpatient care at the hospital at Yale and I cover for other physicians, you know, I try to stay up-to-date, but I am impressed how my knowledge of myeloma has certainly been eclipsed to the

point where I would not refer myself to see me for multiple myeloma, it is just too complicated.

27:04.900 --> 27:37.700 <vNeparidze>It is becoming complicated and really immune drive, in a good way, and with so many different targets and more and more drugs coming down the pike, it is becoming somewhat confusing and generally once again participation in research and clinical trials is encouraged so that we can give the opportunity to our patients to receive something novel, something that will lead to clinical progress and help them going to remission and stay in remission.

27:37.700--> 27:48.500 <vGore> I know a lot of people when they hear about clinical research, they are afraid they are going to be given placebo or sugar pills. Is that something that people should be concerned about?

27:48.500 --> 28:24.100 <vNeparidze>In this country, placebo would not be part of the study unless it is conducted fairly. Generally, most of our phase-I and phase-II trails do not involve placebo and in therapeutic clinical context nowadays in myeloma, it is very rare to have just the placebo as a comparator arm, we would compare it to for instance current standard of care, but I do not think it would be considered ethical to give placebo unless it is part of standard of care to do just the observation.

28:24.100 --> 28:43.000 <vGore>So, you might have the standard drugs you would otherwise use and add a new drug or a placebo to the same drug either way they are getting the same package with either an extra drug that may or may not help or a placebo, so you are still getting the standard drugs.

28:43.000 --> 28:48.800 <vNeparidze>That is correct, they would absolutely still be getting the standard drug for the advanced clinical myeloma.

28:48.800 --> 28:55.000 <vGore> They do not need to worry that they are getting less efficient care.

28:55.000 --> 29:09.300 <vNeparidze>No. I definitely see participation in clinical studies and research as an advantage and as an opportunity for patients which gives them a chance to receive something novel and it helps them and it helps other patients with the same diagnosis.

29:09.300 --> 29:35.000 Dr. Natalia Neparidze is an Assistant Professor of Medicine and Medical Oncology at the 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. We hope you will join us next week to learn more about the fight against cancer here on Connecticut Public Radio.