



Advances in Multiple Myeloma

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Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists, who are on the forefront of the battle to fight cancer. This week it is a conversation about multiple myeloma with Dr. Terri Parker. Dr. Parker is an Assistant Professor of Hematology at Yale School of Medicine and Dr. Chagpar is an Associate Professor of Surgery and the Assistant Director for Global Oncology at Yale Cancer Center.

Chagpar Let's start by you telling us a little bit about what exactly multiple myeloma is?

Parker Multiple myeloma is a type of blood cancer. It is actually derived from plasma cells, and I tell my patients plasma cells are a normal blood component, we all have it, it is just that individuals with multiple myeloma have too many cancerous plasma cells.

Chagpar And what are the presenting symptoms?

Parker People can present in a variety of ways, I think that's one of the things that makes multiple myeloma so interesting as it is very heterogenous in its presentation and how it effects patients. No two individuals may present the same or have the same symptoms. For example, a lot of patients may actually be asymptomatic, meaning this is picked up on routine laboratory studies or symptoms that they present to their primary care physician with or to another specialist. Some of the things that we often see is if someone is tired or has fatigue that could be an indication that the red blood cell count is low or anemia which again can be picked up by symptoms or just a simple blood test if they are having a routine followup appointment with their primary care physician. Other more severe symptoms that we can see are patients who present with kidney failure or an elevated abnormal kidney function, other things can be bone lesions, pain in a specific bone, worst case scenario a fracture of that bone can be some of the more extreme presentations.

Chagpar A lot of people are going to have fatigue and they may have anemia and maybe they are iron deficient or whatever and people may have kidney failure because they are diabetic or they have high blood pressure and people may fracture bones because they are osteoporotic or they are involved in a trauma, how do we know when we should be getting worried about this potential blood cancer?

Parker That is a very good question, a lot of times it is that the individual will have one of these symptoms that cannot otherwise be explained, meaning their doctor has gone through

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the evaluation and they say, your kidney dysfunction is not because of diabetic nephropathy as you mentioned or a high blood pressure. There is really not a good explanation and that is when they kind of look outside the box and say, should we be considering multiple myeloma in our differential or as a cause to these symptoms? Most people do not get that initially, but they will be referred to a hematologist such as myself or one of my colleagues and at that point we do a very thorough evaluation. That evaluation to diagnose an individual with multiple myeloma includes blood work, urine studies, often imaging to look at the bones to make sure we don't see any lesions and then also a bone marrow biopsy is required for the diagnosis.

Chagpar What kind of blood work are you doing, are you doing just a routine CBC?

Parker No, we do very specific tests. We will do a CBC, which is to look for anemia. We will do a comprehensive metabolic panel which looks at their kidney function, their liver function and also the total protein or looking to see if that is elevated and we do very specific studies for multiple myeloma. Those studies include what is known as a serum protein electrophoresis looking at what type of protein it is, is it what we call monoclonal protein, meaning just one type of protein that is being produced. We look at what is called as serum immunofixation. We can look at the quantitative immunoglobulins, serum free light chain, so we can measure all these individual components to really help us put the picture together and we do the same studies in the urine as well.

Chagpar So when you think about that protein electrophoresis which helps you to see whether you have got this peak that would give you a clue that it is multiple myeloma, would you do that automatically or would you do that only if the person has elevated protein?

Parker We will typically do that if the person one has an elevated protein or if they have a constellation of symptoms that is very concerning clinically to us despite a normal protein. We do see some patients who present and do not have an elevation in total protein, but otherwise are textbook, meaning they present with all the classic findings that raises our suspicion.

Chagpar And so, if you had an elevated protein for example on a routine blood test but you are otherwise asymptomatic, your family doctor may refer you to a hematologist if they could not find another explanation for that?

Parker Correct, we will see a lot of people who are asymptomatic, meaning they go and see their primary care physician for the once a year appointment, they are noted to have increased total protein on blood work and that prompts the referral and then some of those individuals we will actually diagnose for something called a monoclonal

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gammopathy of undetermined significance or MGUS which is considered to be a precancerous condition and we do follow these individuals to make sure that there is no evolution into multiple myeloma or progression.

Chagpar So, some people are going to be completely asymptomatic and quite unexpectedly for them they are going to walk out of their doctors' office with an appointment to you, other people are going to have serious problems, they are going to have fractured a bone or they are going to have kidney failure or they are going to have anemia and they are going to be referred to you for the same thing. Either way, they can end up with the same diagnosis of multiple myeloma?

Terri Correct, that is again what I think makes it so fascinating and so interesting to care for as again no two patients are the same and has a very wide range of symptomatology.

Chagpar And so what happens then, they come to you, you work them up, you have done your wide spectrum of blood work and your urinalysis and you come to the conclusion that they have multiple myeloma, what happens next?

Terri Then we talk to the patient about treatments and as you said a lot of times it can be a little bit of a shock to the system for someone who is asymptomatic, so it is important to have a good support system in place, support groups are very prevalent here at Yale, then also throughout the country to really help these patients deal with their diagnosis and then we have a good conversation about what treatment options there are for them. That treatment usually includes a variety of combinations or a variety of medications, typically we will start with a 3-drug regimen and we can consider chemotherapy, but it is a little bit more directed towards the plasma cells.

Chagpar Tell me more about that, what do you mean more directed towards the plasma cells?

Terri I feel that people when they think of classic chemotherapy sometimes they have these nightmares as far as symptoms go. They think of hair loss, they think of bad nausea, bad vomiting, but our treatments do not really elicit those side effects. Because they are aimed to be more targeted to eradicate the plasma cell, we often times do not see kind of those classic side effects that people think of when they hear the word chemotherapy.

Chagpar And are these targeted therapies, we talk a lot on this show about looking for particular genetic mutations and particular genomic changes and then we have got targeted therapies that aim for that particular mutation. Is that the same way in multiple myeloma or is this really more a chemotherapeutic regimen that does not have all of the side effects because it is more targeted to blood cells?

Terri A little of both I would say. We are not to the point as far as targeting specific mutations in multiple myeloma or genetic abnormalities as you pointed out, so this is really targeted to mechanisms and biology in the plasma cell, but it is not specific to one person's cancer over the other, meaning we use the same type of therapy in all comers who have multiple myeloma, so we are not that patient specific yet.

Chagpar And so when we talk about multiple myeloma being a cancer of the plasma cell, one of the things you mentioned as part of the workup is a bone marrow biopsy. Can you talk more about what exactly a bone marrow biopsy is and why that is important, is that where plasma cells come from?

Terri You could say it is their home if you will, where they live. So we do not see plasma cells circulating, or we shouldn't. So the only way to really get how many abnormal plasma cells there are, what is that percentage is to do a bone marrow biopsy. So all the blood work that we do, the urine studies, that is representative we believe of what is going on, because it is a product of that plasma cell that is being produced, but obviously we have to go to the source to really get the answer. So a bone marrow biopsy can get those answers, and because people are very concerned about the pain and have anxiety to do that, typically, we will do a bone marrow biopsy at bedside, meaning we set up an appointment for the patient it is done in the clinic in an outpatient setting. Most people have some minor discomfort following the procedure, but nothing that lasts usually longer than 24 to 48 hours at the site. We always recommend that they have someone there for moral support then most of the time they would be able to drive themselves back, I am just speaking of how things go, because that is a big question people ask how am I going to be able to function and a small sample of the bone itself in the bone marrow is taken from the back of the hip, either the left side or the right side, whatever is best anatomically or if the patient has a preference for it. But the procedure itself takes about 20 to 30 minutes total.

Chagpar So no general anesthesia, no conscious sedation, just local?

Terri Yeah, we just do local, so I often compare it to people going to the dentist and that is what most people say, meaning if you go to the dentist, you get a local anesthetic, so you are awake and you feel pressure and you know what is going on, but it should not be that excruciating pain and that is similar to when we do a bone marrow. It is local anesthetic. You should feel pressure, be aware of what is going on, but it should not be excruciating sharp pain.

Chagpar And so you do the bone marrow biopsy and you talk to the patient about these therapies that are really targeted to the mechanisms pertinent to plasma cells, but that is primarily

chemotherapy. In many other cancers, we talk about surgery and radiation, presumably surgery has less of a role in a blood cancer, but does radiation play a role in multiple myeloma?

Terri Radiation can play a role, and I say can be as it is not something that we will go to upfront because again this is considered a blood cancer, so we need to treat it systemically. However, if a person has a lesion in their bone that is caused by a destruction from the myeloma or if they have a mass that can be known as a plasmacytoma meaning a mass composed of plasma cells, that can be very painful for a patient. If systemic therapy is either not effective or if the lesion is destructive to the point we are concerned about a potential fracture of the bone, then radiation plays a very important role to locally control that area of pain and help prevent fracture. So again it is not something that we would consider in every individual, because everyone presents differently, but if someone did have a plasmacytoma, so again a collection of plasma cells outside of the marrow or a destructive lesion, then we would recommend and work with our radiation oncology colleagues.

Chagpar So multiple myeloma as opposed to many solid tumors is a cancer of the blood, so therefore can it really metastasize, it cannot really metastasize anywhere because it is already in the blood right?

Parker Yes, it is already in the blood, but it can go outside of the blood components or outside of the bone marrow. So people can have what we call extramedullary disease which is disease that has escaped or gone outside of the marrow, and that is when they present with these plasmacytomas. A lot of times, it is more an individual who has more advanced disease who are unfortunately not responding to therapies.

Chagpar We are going to take a short break for a medical minute, but please stay tuned to learn more about advances in multiple myeloma with my guest Dr. Terri Parker.

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This is a medical minute about colorectal cancer. When detected early, colorectal cancer is easily treated and highly curable and as a result it is recommended that men and women over the age of 50 have regular colonoscopies to screen for the disease. Tumor gene analysis has helped improve management of colorectal cancer by identifying the patients most likely to benefit from chemotherapy and newer targeted agents resulting in more patient specific treatments. More information is available at yalecancercenter.org. You are listening to Connecticut Public Radio.

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- Chagpar This is Dr. Anees Chagpar and I am joined tonight by my guest Dr. Terri Parker. We were talking about advances in multiple myeloma. Before the break, we talked a little bit about how multiple myeloma presents and that the treatment really is systemic therapy, but Terri, I wonder if we can take a step back and say who are the people who really present with this disease, I mean is this a disease that anybody cancer, is it a disease of childhood, is it a disease of older individuals, racial predilection, tell me about the epidemiology.
- Parker Multiple myeloma affects all comers, meaning solid tumor and/or liquid or blood cancers is the 14th most common cancer that we see. So roughly about 1.8% of all new cancer diagnoses in the United States will be multiple myeloma. But when we really look at who gets myeloma, it is really a disease of the elderly, the median age at diagnosis is 69, so it is not something that we are seeing in childhood or adolescence, but obviously we do have outliers meaning we do have patients who are in their 30s and this disease has a slightly more male predilection versus female, very slight, and we do see it more common in people who are of African American descent.
- Chagpar And so when these people get multiple myeloma and they are treated with systemic therapy, how are they followed?
- Parker Patients are followed very closely, some would say almost too closely, they have to come in to see us in clinic, but our treatment typically consists of what we call cycles of chemotherapy or cycles of systemic chemotherapy. Now a cycle can vary depending on the type of therapy that is chosen for that individual, but typically a cycle of therapy would be 3-4 weeks from most of our induction or frontline regimens. So most people will be in clinic once a week seeing the nursing team, seeing myself, a physician assistant, for example, to really try to be aggressive in their upfront treatments. Now if a person goes into a remission, we are treating multiple myeloma as more of a chronic disease.
- Chagpar So how do you know when somebody has gone into remission? I mean do you give a certain number of cycles and then do a blood test to see whether the protein count has gone down or do people get routine blood work at every cycle, how does this all work?
- Parker That is a good question. We will do blood work at the start of each cycle of therapy, because obviously we do not want to treat somebody if it is not effective and we want to make sure we are really benefiting the patient with this treatment. So, we will typically check the same labs that we did for diagnosis prior to each cycle of their treatment, and we have very strict definitions as far as what kind of reduction do we need to see to label

someone in remission. So we need to make sure that we eradicate that protein from the blood to even begin to think about a complete remission and a bone marrow biopsy would be required again to make sure we do not see any abnormal plasma cells.

Chagpar So you do this blood work, you do not see any plasma cells, you get another bone marrow biopsy, you do not see any plasma cells and then you say to the patient congratulations, you are in complete remission?

Parker But we still need to treat you.

Chagpar But we still need to treat you, tell me more about that because I mean I can perceive that the patients would say woohoo, complete remission, I am home free, and you say not so fast.

Parker Typically we have a few different routes we can take, so if someone gets induction therapy, we tend to treat them first with a number of cycles, again I was talking about that 3-4 week period, is considered a cycle. We will often then, depending on the patients age and their comorbidities, meaning what other medical problems do they have, evaluate them for whether or not we think an autologous stem cell transplant is in the cards. I personally do not transplant patients, but they work closely with some of my transplant colleagues here to make that decision.

Chagpar Let's talk about that, what exactly is autologous stem cell transplant and when would somebody think about doing that, because so far we have really talked about just chemotherapy.

Parker With autologous stem cell transplant the stem cells that are collected are the patient's own and so the purpose of it is to be able to give higher doses of chemotherapy, so typically a person may get induction or frontline therapy, several cycles, averages of 4-5 and then they would be given a medication to try to stimulate white blood cell production to collect stem cells. Those stem cells are their own. Stem cells can grow up to be any cell that they want. The stem cells can either be frozen and reserved for another day or the patient can then go through high dose therapy and then they are given their stem cells back to shorten the period where they really have no cells, so to shorten the period that they require transfusion support, shorten that period that there are increased risks for infection.

Chagpar Does everybody need a stem cell transplant, what if you give people induction chemotherapy and you found that they went into complete remission, does that ever happen?

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Parker That can happen and then we would recommend collecting the stem cells, that way we have them. The more therapy someone gets, it may be harder to collect their stem cells say several years later, so we tend to always encourage stem cell collection, but if someone were to go into a complete remission just with their induction therapy, we can then proceed to what we call a maintenance therapy to try to maintain that response and save the stem cells for a future date if they are ever required. So even if you get a complete remission, you still need this maintenance therapy which is chemo, so it is a type of chemo, so we do believe that people do benefit from maintenance in our studies, although people do have an improvement in their survival when they are placed on maintenance versus nothing and so here in the United States, we believe in maintenance in most individuals unless there are extenuating circumstances, intolerance will go onto a maintenance regimen, but maintenance regimen is often a medication they have seen in the induction period, but instead of 3 drugs, we use one and at much lower doses.

Chagpar But they are still going to get therapy every 3-4 weeks right, every cycle?

Parker When we go onto maintenance, we try to use an oral medication and again it can vary from patient to patient, but medication for 3 weeks in a row, then a week off. So then people are coming to clinic once a month, so it is not as strenuous as that once a week appointment depending on what treatment they are getting, but we really do tell individuals that we are trying to treat this as their chronic disease similar to say if they had high blood pressure or diabetes, they would be on some medication to control that disease and then coming in with routine follow-ups and check ins to make sure that medication was still effective and they were not having side effects from the treatment.

Chagpar So it is good that it is an oral medication, because I can imagine that if it was IV chemotherapy that would be kind of a bummer.

Parker Yeah, that would be very stressful. In some individuals who are high risk, we do tend to give them a subcutaneous injection, so it is a little bit more intensive as far as coming to clinic, still having treatment, but we try to do the least invasive as possible obviously keeping in mind quality of life and lifestyle for the patient.

Chagpar Speaking of quality of life, let us talk about quantity of life. How long do patients with multiple myeloma live? What is the prognosis?

Parker We are actually doing much better in that regard, if you look at data compared to the 1990s to now, the 2000s and beyond, we have improved what we call our 5-year overall survival, meaning the number of patients who are still alive at that 5-year mark and again

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this is probably a little bit outdated data, but if you look at the data that is kept, the 5-year survival currently is about 50%, but again that is looking at patient data up to 2012, 2013 and we just had 4 new drugs approved in 2015, so we are having a lot more advances, a lot new medications, so I anticipate that you will see that number continue to climb as we get the new data coming in.

Chagpar Tell me more about these new treatments and new advances, we often talk on this show about clinical trials and how important they are and all of the new advances coming out, what are the most exciting things in multiple myeloma?

Terri As I mentioned, in 2015, we had 4 drugs approved by the FDA for multiple myeloma and those drugs were monoclonal antibodies so again more targeted to cell markers or pathology within the plasma cell. We then had 2 other drugs ixazomib and panobinostat, so that was 2015, now it is 2018, so as you mentioned we really need to continue to do clinical trials, continue to do research both in the upfront setting and in the relapse refractory patients. Despite all these advances, we still have people who progress and we still have unanswered questions as if most cancer drugs when they are approved they are approved initially in the relapsed refractory setting and then slowly make their way to more upfront treatment and so lot of the trials now are trying to answer questions like what is the best order for these medications now that we have options, should we be using them, or should we be moving them to the upfront setting?

Chagpar We talked a little bit about autologous stem cell transplant and one question that people might have is, you are taking people's own stem cells, you are treating them, so you are depleting their cells and the idea is that you give them back their stem cells so that they can then recover and make new cells, but their cells ended up getting cancer, so how often is it that after an autologous stem cell transplant your stem cells that you had before that you now got back ended up getting cancer again?

Terri We do tell people that autologous transplant is not a cure for this disease and if the patient's cancer comes back it is usually because we do not eradicate all the plasma cells that are there, not that that stem cells necessarily bad stem cell. We often consider plasma cells, some people refer to them as the cockroaches of the bone marrow, meaning they are really hard to get rid of when we give ablative chemotherapy, so really high doses of chemotherapy say to another patient who has leukemia when we look in their marrow what we often see is plasma cells and so when people have disease that comes back after autologous transplant it is because they still had a cell that was there.

Chagpar And not because the autologous stem cell was a bad stem cell?

Parker Correct.

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Chagpar So how often do people relapse?

Parker Again, most people when we put them through a transplant we are trying to improve their response, meaning they may not be in the complete remission, they have may have had a partial remission which is a 50% reduction in their protein or what we call a very good partial remission which is a 90% reduction in their protein. So we are trying to improve upon that, meaning get them hopefully to a complete remission if we can and then the next step would be eradicate any minimal residual disease which we look at via the marrow, but even if we do that, we still tell patients that it is not a cure but a remission and there is a percentage that can come back. We often do not call a specific percentage because it is very variable depending on the person's risk and how they responded to their therapy to begin with.

Chagpar So once a person gets a complete remission whether or not they have had an autologous stem cell transplant, you put them on maintenance and then you continue to follow their blood work and for some as yet undefined proportion of those patients their cancer will come back?

Parker Yeah and it is a hard thing to say because I have some patients who have been alive for 20 years with multiple myeloma, but then we have some patients who have very aggressive disease, very poor risk cytogenetics meaning just the biology of the plasma cell or that clone that is driving things, just does not respond to any treatments and they do not live a year, so that is why we try to look at how the person responds, what are they presenting, are they presenting with a lot of disease outside of their marrow to begin with, do they have poor risk features that we think is going to make them more resistant to our treatments.

Chagpar What are those poor risk features?

Parker Poor risk features that we look at are defined by our cytogenetic, so that is part of another reason why we do the bone marrow biopsy in individuals to start and anytime that there is a progression because we would want to see is it a different clone or have they acquired any new cytogenetic abnormalities. So the ones that we are looking for associated with the poor risk is something called a deletion 17P, meaning they are missing that part of their 17 chromosome and a translocation between chromosomes 1416-1420 and amplification of 1Q, so this is a very specific cytogenic abnormalities that we look for in every individual.

Chagpar And so if they have these, that is a clue to you that this is a bad player, but do we have novel therapies that can then target these particularly bad players?

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Parker Yeah, so that is a good question and something that is still being worked out, so right now we do not necessarily treat those individuals any differently upfront, although there are clinical trials that are ongoing specifically in those high risk individuals to try to answer that question, for example, should we be doing 3 drugs or 4 drugs, adding new novel therapies to try to come up with that and we also tend to be more aggressive on the backside meaning in those individuals are maintenance therapy maybe include consolidation, meaning additional cycles of what they got in induction and we may again keep them on a more aggressive regimen that includes 2 to 3 drugs versus that one drug.

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