

Yale CANCER
CENTER
answers

WNPR Connecticut Public Radio



Hosts

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**Using the Immune System to
fight Multiple Myeloma**

Guest Expert:

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Medicine in Hematology; Professor of
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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. Foss and Dr. Chagpar welcomed Dr. Madhav Dhodapkar. Dr. Dhodapkar is the Arthur H. and Isabel Bunker Professor of Medicine in Hematology, Professor of Immunobiology, and Chief of the Section of Hematology at Yale School of Medicine. Here is Anees Chagpar.

Chagpar Let us start off by having you tell us what it is that you do and what myeloma is?

Dhodapkar Myeloma is a cancer of plasma cells and these are cells that make antibodies that help us fight infections, but every so often a cell will become a rogue cell and start growing in the body, most commonly in the bone marrow, and that leads to formation of what we call holes in the bones or lytic bone disease and these people get anemia and infections and things like and it is a significantly aggressive malignancy. About 10% of all people with blood cancers are estimated to have myeloma and there are about 14,000 new cases diagnosed a year, so it is a fairly common malignancy involving blood cells that grow in the bone marrow.

Chagpar Madhav, if you are a person who is listening to our show and thinking about blood cells and cancer you think about how this presents, do these people present with anemia and fatigue and infections? How would you know if you might have myeloma? If you have a breast lump, you think breast cancer, but is it more difficult to diagnose?

Dhodapkar Quite often it is true that a lot of people do have fatigue, bone pain, and infections at initial presentation, but it is also equally common that these things get picked up as part of a routine health evaluation when blood tests are done as a part of regular health maintenance and people find abnormalities in protein levels and those protein levels are abnormal because the myeloma cells make these abnormal immunoglobulins or abnormal antibodies that get picked up on these blood tests. At least a third of patients that we find in the clinic today are completely asymptomatic, or had no symptoms at the time they were diagnosed.

Chagpar So, you go in to see your doctor for your annual physical exam, you are feeling great, they run a blood test and they say, "Hmm, I am seeing these abnormal proteins." Is that when people come to see you?

Dhodapkar Correct, the most common next step at that time is for the internist or the primary care provider to refer the patient to a hematologist, the kind of physician that I am, and then we would go through a battery of tests to actually ascertain the significance of that abnormality and those can include a simple blood test initially, but also in some cases x-rays or bone marrow biopsies to ascertain

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whether or not the increase in the protein is a result of an abnormal increase in the plasma cells and is that enough to meet the criteria for what we call myeloma, because the great majority of times we see these abnormalities and the entity is benign and so it is very important to be able to be seen by a hematologist so that one can accurately prognosticate what course that entity is going to take.

Chagpar Because it would be very different if you said, well you know this is a completely benign entity versus this is myeloma.

Dhodapkar Correct.

Chagpar Let us suppose somebody comes in and they see you and go through your battery of tests and x-rays, and you figure out that this is myeloma. What is that person's prognosis?

Dhodapkar We have been very fortunate that over the past decade there have been several new therapies that have come about in the care of myeloma patients, again emphasizing the importance of clinical research and introducing new therapies into the care of a disease that was as difficult to treat as myeloma was about a decade ago, but with the introduction of these new therapies we are able to get the great majority of patients, over 90% , to achieve a response to therapy, meaning a reduction in protein levels, reduction in the plasma cell burden and for the first time now we are actually able to see people live five or ten years after a diagnosis which is something that we could have never imagined when I started working in this field. On average when we take 100 patients with myeloma, we still assume that the median survival, or the average survival, is in the range of five to seven years, but that is twice what it used to be just a few years ago.

Chagpar Tell us a little bit more about what these therapies are like and what are some of the new advances that have helped us to see that improvement?

Dhodapkar Some of the therapies that have become the mainstay of treatment of myeloma now fall into two broad categories, one is a set of therapy that is called immunomodulatory drugs, or IMEDS, and the pair and compound in this class was a drug called thalidomide, which I am sure the listeners are quite familiar with. But some of the newer generations of medications in that category of drugs like lenalidomide or pomalidomide, more recently, and the second major category of drugs is a drug that targets the garbage disposal system of the cell called a proteasome inhibitor and the classic drug for that initially was a drug called Velcade, or bortezomib, and the combination of these medications has now allowed us to achieve very high response rates for initial therapy of myeloma. Again, what is perhaps even more exciting I think is that there are several drugs now in addition to these that are also showing promise in early phase studies and the hope is that the combination of these newer medications, along with newer advances in therapy and the ability to understand different kinds of myeloma that occur in different patients, will allow us to personalize individual therapy and tailor therapy to each individual patient appropriately.

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- Chagpar Tell us a little bit more about what these newer classes of drugs are and how that whole interaction works?
- Dhodapkar The IMEDS, or the immunomodulatory drugs, are thought to work by having several effects on the body, particularly on activating the immune system, hence the name immunomodulatory drugs. They also affect a process called angiogenesis, which is a formation of new blood vessels that is thought to be important for most cancers to grow and the second class of drugs, proteasome inhibitors, simply appear to work by shutting down the garbage disposal, if you will, of the cell and cells such as myeloma cells which make a lot of protein are dependent on such a disposal system to work well, and because of that they are particularly susceptible to these medications and we are able to achieve very rapid reductions in tumor burdens with the combination of these medications. What we are learning, however, is that we have a much better handle now on the genetic blueprint of these tumors. We understand the nature of mutations that occur in most myelomas, the kind of abnormalities that occur in most myelomas and the next wave of therapeutics that we think is going to be built on in this initial success is going to depend on targeting specific therapies based on the kind of abnormality that we think is driving that particular kind of myeloma. And so while I think we have been successful in getting a very good initial handle, if you will, on this disease, I think none of us in the field really want to rest on these laurels, but rather build on this to take it to the next step, which is our ultimate goal of trying to cure this disease in the majority of patients.
- Chagpar Do you think that is possible?
- Dhodapkar I remain optimistic that now that we actually have a much better handle on the blueprint of this disease and a much better handle on understanding the different kinds of myeloma that exist, that we will actually have the ability to tailor things to individual patients and try to get high rates of response in remissions without much toxicity.
- Chagpar Is the idea behind personalized medicine that you will be able to do a bone marrow biopsy or take a blood sample and identify these myeloma cells and find the genetic mutation in an individual patient and then tailor that therapy for that mutation, so that you will have different therapies for different patients?
- Dhodapkar We are actually beginning to do some of that at Yale now. When patients get diagnosed with myeloma at Yale, for example, we are trying to undertake a very detailed analysis of the genetic level, and that includes sequencing of the genome, for example, of the myeloma cell so that we not only understand the nature of abnormalities, abnormal pathways, abnormal connections within the cell that make a cell the common rogue cell, but then that provides us the opportunity to ask questions about the feasibility of targeting those specific abnormalities and there are drugs being

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developed by industry in different categories. The other thing that I am particularly interested in is that every mutation that leads to an abnormal protein made by a cancer cell makes it a target for the immune system and so as we know about the kind of mutations that exist in a myeloma cell and we precisely know where those mutation are, we can in fact begin to target those very mutations with the immune system without even having a drug available for that mutation. So those sorts of things are now finally becoming a reality because of the ability to access this new technology and the understanding of how the immune systems acts against tumor cells and how we can actually unleash the power of the host, if you will, against these abnormal cells.

Chagpar So essentially you are helping the body to fight this cancer by itself?

Dhodapkar Correct, I think what we have learned over the years, and this was first learned in the context of patients, those precursor states we talked about earlier, the kind of people who are actually feeling well, they get picked up by the primary care provider and we tell them they have a benign entity. It turns out that even these people with so called benign entities actually have cells with a lot of mutations and we are learning now about the kind of things that the body can do to control these or keep these abnormal cells under control, and I think if we harness this very same thing in people who fail to do so, I think there is a potential that we might actually have the ability to control disease for a long period of time and turn it into a chronic illness or even achieve a cure.

Chagpar Potentially, if you have cells that have mutations, but they have not quite turned into a cancer cell and you can identify these mutations and you can make the immune systems prevent those mutations from becoming cancer, potentially we have even got a preventative therapy?

Dhodapkar Correct, and a lot of what we are excited about now is the feasibility of actually taking that step. In fact, very recently we completed one of the first preventive trials here at Yale to try to learn how to prevent myeloma in high risk populations and while this is a process that will take several years to really understand how we can benefit the whole population at large, the initial steps are simply to understand whether or not we can take people with high risk of progression and prevent that high risk of progression to occur into clinical myeloma, and those approaches are in fact based on both drugs such as the ones we use to treat myeloma but also based on immunologic interventions.

Chagpar That is incredible. We are going to take a break for a medical minute, please stay tuned to hear more about using the immune system to fight multiple myeloma and potentially other cancers with Dr. Madhav Dhodapkar.

*Medical
Minute*

This year over 200,000 Americans will be diagnosed with lung cancer and in Connecticut alone there will be over 2000 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

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advanced therapies and specialized care. New treatment options and surgical techniques are giving lung cancer survivors more hope than they have ever had before. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale, to test the innovative new treatments for lung cancer. An option for lung cancer patients in need of surgery at Yale Cancer Center is a video-assisted thoracoscopic surgery, also known as VATS procedure, which is a minimally invasive technique. This has been a medial 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 co-host Dr. Francine Foss and our guest Dr. Madhav Dhodapkar. We are discussing how we can use the immune system to fight multiple myeloma. Just before the break, Madhav you were telling us about how you can potentially grab up the immune system and help it to even prevent cells that have mutations that have not become cancers as yet in myeloma from becoming myeloma and one of the questions that I have, and I am certain that all of our audience has, is, is there the potential one day to take what we have learned in myeloma to other cancers?

Dhodapkar Absolutely, I do think that there is potential and there are several people working to try to understand this whole process, but I think what is important is that some of the technology that is now real and that is available, particularly at major centers like Yale, allows us to in fact ask questions that we could have never dreamed of as early as two years ago and these things allow us to have not only the genetic blueprint of the tumor cells at hand as we see the patients, but also to understand and predict which parts of that genetic blueprint are amendable to targeting by the immune system, and that can, for example, allow us to take the next step which is the potential of creating a patient specific individualized vaccine based approach. The other thing that I want to point out though is that one of the big surprises, particularly in the last couple of years, has been that we have learned that the immune system in fact is already constantly in battle with cancer and one of the big problems is that there is always a break on the immune system and for many years we actually tried to press on the gas pedal only to realize that one of the key things we have to do for the immune system to work is to take the foot off the brake and if we learn to do that appropriately, we will actually avoid a lot of the problems about immunity but at the same time, kill tumor cells and actually this leads to some very impressive responses particularly in diseases like melanoma, lung cancer, and kidney cancer where many of the studies actually done at Yale have been very instrumental.

Foss Madhav, can you tell the audience how you take those laboratory observations and those observations from the genetics and move them into the clinic and how you are impacting the disease?

Dhodapkar This is a bidirectional dialogue. In a sense that we are always learning from our patients in terms of how the disease presents itself and what the tumor cells look like and the impact our

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interventions have on the disease. The ability to study tumor cells at very high levels, high resolution in the laboratory, coupled with the development of new models to actually understand the biology of the cells in mice, has allowed us to really understand what the change is in the genetic blueprint, how they translate, if you will, to the abnormalities in tumor cells and that has allowed us to be more logical about the next steps, which is trying to target the Achilles heel of different cancers. For example, if one were to find abnormalities in the cancer cell that one thought would be potentially targetable by a drug, one could now in fact test that in a laboratory in an animal model before one tries to test that in the patient, which substantially improves the likelihood of being able to predict success.

Foss How close are you in multiple myeloma to be able to do that for patients?

Dhodapkar We have actually been fortunate that many of the technologies that we are talking about are either already in place or at very advanced stages of development and we were fortunate to receive a large innovator award a few years ago from the National Institutes of Health to actually develop such models and that work has been very successful in terms of developing these preclinical models that predict the likely response to a drug or to an intervention and so I would believe that the next set of studies that we would anticipate doing at Yale over the next few years would actually be just that.

Chagpar So, once you have this great preclinical model and you have these mice who you have given myeloma, and you can find their genetic mutations and you can target that, how do you take that and then test it in patients? Are there clinical trials available now that patients can benefit from these preclinical studies?

Dhodapkar That is a great question because I think if there is one thing I would like to emphasize for this session it is the importance of clinical trials. We really could not have made the advances that we made without participation in clinical trials and I can tell you that we were fortunate years ago to help introduce thalidomide, which is the first drug to be part of this initial wave of therapeutics in myeloma, but none of that would have happened without a clinical trial and here at Yale we are engaged in several active clinical studies that involve some very new promising drugs. Some of those drugs are in advanced phases of clinical testing now and we expect and hope that some of those will in fact even get FDA approval for meeting a certain defined need for care of myeloma patients but there is no question that there are a lot of promising therapies that exist as accessible only through clinical trials and I would certainly encourage patients to always ask their physician as to what clinical trial they are eligible for at all stages of their care.

Foss In all of these clinical trials, oftentimes we get samples from patients, we get tumor samples and we study them directly. I wondered if you could tell the audience how important that is because we always ask that question, can I take a sample of your tumor? Or, will you give me an extra tube

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of blood? And you are the kind of scientist that benefits from that, so could you reiterate to our audience how you actually use that material and how important it is?

Dhodapkar So inherent in the clinical trial is the unpredictable nature of whether or not a person will respond to that therapy. We really do not know what the likelihood is of response, otherwise we would never actually do a clinical trial and so it is equally important for us to understand both the successes and the failures. If a person were to respond to the therapy we would want to know why he responded and if a person did not respond, we would equally want to know why he did not respond because it is through that sort of dialogue that we can actually advance the field. So, while it is important for patients to be on clinical trails, I think the benefit of the clinical trial to both the patient and society is substantially enhanced by trying to understand why patients' benefit when they do and why they do not so we can keep advancing the field.

Chagpar So many patients opt to participate in clinical trials precisely for that, so that we can advance the field and advance the knowledge and help society, but it seems to me that if you have done this preclinical testing and you have started to figure out these genetic mutations and how to help the immune system to target them and you have tested them in animals, and you were telling us before the break how life expectancy with myeloma has doubled. So, clearly the patients who participate in clinical trials would presumably do better themselves than they would off a clinical trial?

Dhodapkar Correct, I think one of the common misconceptions about clinical trial is that they simply represent unproven therapy and I think that is wrong. What clinical trials often represent is in fact state-of-the-art care for that patient and the reason for that is that a lot of trials, actually all trials, have to go through a committee of people that includes physicians, other health care providers, and even patients to try to ascertain that the risk-benefit for that trial actually strongly favors the benefit and that there is nothing better that can be done for that patient at that time. So, one of the advantages of a clinical trial is that this is an opportunity to actually have the most state-of-the-art care available as of that moment.

Foss Madhav, do you believe at this point that we know what the best standard of care is for multiple myeloma or do you think that the drugs that we are using that we think are the best, may not be the best after your research? For instance, shows us some of the interesting pathways that we should be targeting.

Dhodapkar In an ideal scenario my dream is that we treat people with the least toxic medications possible with the highest durable likelihood of cure. I think that is the dream of every oncologist and my view is perhaps not unique for that, and we're not there yet. So, until that happens we have our work cut out for us, and until we get to that goal, it is not just a matter of cure, but cure with the least likelihood of long term side effects is where we need to be.

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Foss And most myeloma patients are older so they do not tolerate a lot of the very aggressive chemotherapies that we can give to younger patients.

Dhodapkar Correct.

Chagpar We talked a little bit about state-of-the-art therapies and clinical trials and genomic sequencing and it seems to me that a lot of this is really hi-tech. Is this something that if you go to your family doctor, if you live in the middle of a rural county and your doctor finds that you have this abnormal protein, is this something that you should be looking to go to a large center for? Is this something that can be treated locally in a smaller center? Give our audience a perspective on how common this is and where therapies are in terms of what you can get at different types of centers.

Dhodapkar It is true that perhaps five years ago some of the stuff I am talking about could have been considered science fiction, but many of the major cancer centers, Yale being one of them, are investing a lot of resources in trying to create the right kind of infrastructure it takes to better understand this blue print of cancer and I think that sort of makes the case for patients to try to gain as much knowledge about that specific cancer and that particular individual. In the end it will take a partnership between an oncologist in the community and an oncologist at a referral center to really create the best form of personalized medicine, if you will, for that patient, because no one group can actually do the entire thing. But I think we are getting closer to doing that not just through our colleagues within our own group here, but also with the help of the care centers who are affiliates in the community and trying to hopefully deliver the best quality of care possible.

Foss One of the treatments for myeloma has been to do a transplant, and we thought that was the best way to keep patients in remission. Could you comment on that and tell us if you think some of these new approaches might make transplant a thing of the past?

Dhodapkar It still remains an option for many patients and it is certainly utilized in the care of myeloma patients as of 2012, what will happen five years from now is an open question. What has changed is that the timing of the transplant has become more of a question than it was in the past and it is not uncommon for us to collect stem cells and defer the transplant to a later time in many individuals. We like to make that decision, at least at Yale, based on the kind of myeloma, the aggressiveness of disease and the other options available to that patient. So, to answer your question more directly, I think transplants still remain one of the things that we would do for myeloma patients, but its role has evolved into somewhat of a different role than it was say 5 to 6 years ago.

Dr. Madhav Dhodapkar is the Arthur H. and Isabel Bunker Professor of Medicine in Hematology, Professor of Immunobiology, and Chief of the Section of Hematology at Yale School of Medicine. If you have questions or would like to add your comments, visit yalecancercenter.org where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.