

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 1888-234-4YCC. This week, Dr. Foss welcomes Dr. Michael Dickinson. Dr. Dickinson is a consultant and hematologist at the Peter MacCallum Cancer Center in Melbourne, Australia. Here is Francine Foss.

Foss Let's start off by having you tell us a little bit about what you do, your position, and what kind of cancers you take care of.

Dickinson I am a hematologist, so I take care purely of cancers of the bloodstream and of the bone marrow. I work in a cancer center in Melbourne called the Peter MacCallum Cancer Center. This is a referral center where we see new cases, but also provide second opinions for patients with hematological malignancies. My practice is very broad, so I see all kinds of hematological malignancies, but I have a particular focus on multiple myeloma as well as T-cell lymphomas, and also I do a bit of work in myelodysplasia as well so it is a fairly broad range of diseases.

Foss Let's talk a little bit about the spectrum of bone marrow cancer. Tell us about the bone marrow itself, what it does and what kinds of cancers can arise from the bone marrow.

Dickinson When I talk to patient's about the bone marrow, I describe it as being the factory of blood cells, and not all bones contain bone marrow, most of the marrow is contained in the pelvis and some in the bones of the back. The marrow itself has fat in it, but it also has these precursor cells, and sometimes when we look in the marrow we see cells that we never see in the bloodstream and when I talk about the cells in the bloodstream I am talking about the red cells, the white cells, and platelets. In the bone marrow, we have precursors for all of those types of cells and there are also lymphoid precursors, so the lymphocytes as well, and broadly speaking, the cells in the marrow we break down into the myeloid precursors and the lymphoid precursors and there are some cancers of the blood stream where we only find those cancers in the bone marrow when we take a look and see.

Foss And there are stem cells in the bone marrow as well?

Dickinson That is right. When I am talking about the precursors, I guess I am also referring to the stem cells, which are the most immature cells which can make all different types of cells depending on what kind of stem cells they are, but there are stem cells that we are used for stem cell transplantation.

3:15 into mp3 file <http://yalecancercenter.org/podcasts/2013%200127%20YCC%20Answers%20-%20Dr.%20Dickinson.mp3>

Foss How does a patient know that they have a bone marrow cancer or something wrong with the bone marrow? What would the initial clinical manifestations or lab abnormalities be?

Dickinson It depends a little bit on the kind of cancer, but for many patients they have no symptoms at all and a cancer of the bone marrow or abnormality of the bone marrow that is not a cancer can be picked up on while doing a blood test, just a simple full blood count where there might be too many of a particular type of cell, or too few of a particular kind of cell. Whether the shape and size of the cells is different from what we expect to see, is what might be a hint to a doctor to perhaps take a closer look at the bone marrow. Some patients will have symptoms and those symptoms will be symptoms of either low or high red cells, low or high white cells, and low or high platelets, and probably the most common symptom is fatigue, in the case of anemia, which is low red cells. Some patients have infection as a consequence of low white cells and some patients have bruising as a consequence of low platelets and it those are the sort of symptoms we often see, but there is a whole range.

Foss In order to make a diagnosis of a bone marrow cancer, you have to do a bone marrow biopsy, and that concept scares a lot of patients when we mention it, can you talk a little bit about what that is, is it as painful as they say it is?

Dickinson A bone marrow biopsy is a scary idea, but it is absolutely a routine part of our practice. We do 100s of them a year at Peter MacCallum and most patients will have many of them as part of their routine care, and so as a consequence the person who is doing a bone marrow biopsy is usually very experienced at making it a very well tolerated procedure. We generally use a local anesthetic and that always stings a little bit, for a couple of seconds, like a brief beesting. The marrow that we biopsy is in the pelvic bone and people often think about a bone marrow biopsy as being near the back or near the hip, and it is not really near the back or near the hips, it is in this big pelvic bone it is very safe, it is away from major organs and very low risk and there is always

the sting of the local anesthetic, but after that there is very little pain and it takes a couple of minutes to do, really only 3 or 4 minutes and all of the time is in the set up and preparing the slides afterwards. We use a small needle and we take a sample of blood first and we take a liquid sample of the marrow using a syringe and then we take a very-very tiny piece of bone marrow core, which is about half the size of a matchstick, if you think it about it in terms of size, and I find that most patients tolerate it very well and have no problems after the procedure at all. Some patients feel just a little bruised but really it is very-very well tolerated and you only have a very tiny little scar, if any scar at all.

Foss We are now doing a lot of sophisticated testing including molecular testing. Can you comment on how we actually make the diagnosis of bone marrow cancers, what are the spectrums of tests that we are doing in the lab now?

6:47 into mp3 file <http://yalecancercenter.org/podcasts/2013%200127%20YCC%20Answers%20-%20Dr.%20Dickinson.mp3> Dickinson I think the absolute core test is still the blood test and the pathologists look at what the cells actually look like in the bone marrow, so it is still the most important test, a doctor looking down a microscope and looking at the shape of the cells and the number of the cells to see if there is something wrong, that then guides what sophisticated test we should then do. That is still the core of how we make that diagnosis. The sophisticated test includes flow cytometry which is where we use dyes that are mixed with the cells and they target particular proteins on the surface of cells and they guide us to what kind of cancer we are looking at, and that is very useful in diagnosing leukemias in particular, and lymphomas as well. Sometimes we can use those dyes and actually look at the cells and place them under the microscope, but a flow cytometry machine does the counting of the cells for us and that helps us subdivide the kind of lymphoma or leukemia that we are looking at and also helps rule out those diseases. We would often use flow cytometry in routine care of patients with leukemia to make sure that the leukemia has been cleared from the marrow after treatment, and that is true also with something like multiple myeloma, we use flow cytometry for that. You mentioned some of the sophisticated molecular tests and these are again very useful in leukemias and also lymphomas. There are tests where we use fluorescent antibodies to look at the genes inside the cancer cells to tell us if they are rearranged or not. Those tests have been around for many years and they are sometimes referred to as FISH, and then there are the most sophisticated molecular tests where we use modifications of polymerase chain reaction and often specially designed instruments to look for particular abnormalities and which test we do usually still comes back to what the

Dickinson I think it is fair to say that the frequency of these cancers is relatively stable and they are relatively rare cancers when compared to cancers like breast or lung. If we look at myeloma now and as it was 10 years ago, the rate of it has not increased very much and there is no suggestion that there are epidemics of that occur. It seems to be relatively stable over time and relatively infrequent. As you mentioned, it is more common in older the population, increasing in frequency as we get older, age 50 and up towards 65 years of age it becomes increasingly frequent.

Foss What about risk factors for multiple myeloma? I know with certain kinds of leukemia we have talked about benzenes and chemical exposures and radiation exposure. Is there anything, or are there any specific exposures that are associated with multiple myeloma?

Dickinson Not really, certainly in an individual case everyone asks why me, and in multiple myeloma really more than any other cancers we do not know, and there have been links again with chemical exposure and benzenes and also with radiation and myeloma, but the links are fairly loose and it is not really very well understood why myeloma arises.

Foss We have to take a break for a medical minute. We are talking to Dr. Michael Dickinson about bone marrow cancers and multiple myeloma.

Medical

Minute This year over 200,000 thousand Americans will be diagnosed with lung cancer and in Connecticut alone there will be over 2,000 new cases. More than 85% of lung cancer diagnoses are related to smoking and quitting, even after decades of use, can significantly reduce the risk of developing lung cancer. Each day patients with lung cancer are surviving. Thanks to increased access to advanced therapies and specialized care, new treatment options and surgical techniques are giving lung cancer survivors more help than they have ever had before. Clinical trials are currently underway at federally designated Comprehensive Cancer Centers like the one at Yale to test 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 a VATS procedure which is a minimally invasive technique. This has been a medical minute. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

14:44 into mp3 file <http://yalecancercenter.org/podcasts/2013%200127%20YCC%20Answers%20-%20Dr.%20Dickinson.mp3> Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my guest Dr. Michael

Dickinson. Dr. Dickinson is from Melbourne, Australia and he is joining us today to talk about bone marrow cancers, and specifically multiple myeloma. Michael, we talked a little bit in the earlier part of the show about bone marrow cancers in general. Let's focus now on multiple myeloma. Again, we mentioned that this is a disease of older people. Can you tell us a little bit about how it presents and what the treatment options are for this kind of cancer?

Dickinson Multiple myeloma is now generally diagnosed earlier in the course of the disease than it was say thirty years ago. Multiple myeloma is a cancer of plasma cells and plasma cells usually live in the marrow and in the bone itself either diffusely or in patches. It is sometimes in small tumors in the marrow itself or in the bone itself. Plasma cells are part of lymphoid system, the very mature lymphocytes produce something called paraprotein which is really an antibody gone wrong, and we all have antibodies to help us fight infection. It is a protein in the blood that attacks infection. In myeloma, these plasma cells produce an abnormal antibody called a paraprotein. Myeloma can cause a number of different symptoms and those symptoms relate to the effect on the bone marrow, to the effect on the bone itself and to that paraprotein. Starting with the bone marrow, I mentioned earlier that one of the things that we look for on the blood test is anemia. Anemia is when we have low red cells and red cells are used to carry oxygen, and so patients with myeloma will sometimes present with anemia. Now there are lots of causes for anemia. Not everyone who has low red cell counts should worry that they have myeloma, but myeloma can present with anemia. The other consequence of myeloma is its effects on the bone and in multiple myeloma some patients, but not all patients, will experience a relatively rapid form of osteoporosis, thinning of the bones with fractures and so some patients present with a fracture of a bone that has occurred with minimal trauma, and on x-ray the bones look thinner than we expect. Again, people with osteoporosis should not worry that they have myeloma, but there are some cases of very localized osteoporosis or very advanced osteoporosis where myeloma is contributing to what is happening and so bone pain is one of the things as a consequence of fractures that patients can present with. I mentioned the paraprotein. Now the paraprotein itself rarely causes symptoms in most patients, but in a subset of patients, again, not all patients, they can affect the kidneys and so some patients will present with abnormal kidney function. Another consequence of the effect of plasma cells or myeloma cells on the bones is that as the osteoporosis process gets out of control, the bones can leach calcium and that can cause dehydration and contribute to the kidney problems. In some cases it is something that is picked up on just a simple abnormal blood test when there are no major symptoms and a bone marrow is done to investigate an abnormal blood count in low and behold there's multiple myeloma.

Foss What are the treatment approaches for patients once you make the diagnosis of myeloma?

Dickinson The treatment approach really depends upon the patient's age and fitness and any other medical problems. So we obviously tailor what we do to the individual, what we feel they are able to tolerate and what we feel will provide the best effect for them. Now in Australia, and in my

19:37 into mp3 file <http://yalecancercenter.org/podcasts/2013%200127%20YCC%20Answers%20-%20Dr.%20Dickinson.mp3> approach is still to incorporate autologous stem cell transplantation in patients where we feel that is feasible and we offer autologous stem cell transplantation in many patients up to and sometimes over the age of 70, I'll come back to what that is, but usually what we do is we try to treat the myeloma when we see it. We tailor our choice of treatment around which of the organs are most affected and it is usually a combination of chemotherapy with one of the novel antimyeloma agents and that will either be something like thalidomide or Revlimid, lenalidomide or Velcade usually in combination with chemotherapy and the chemotherapy that we use will depend a little bit on the protocol that we choose, sometimes it is given intravenously, sometimes it is given orally. It is usually a very well tolerated treatment, but it increases the response rate of those normal therapies so my approach is to try to get the myeloma under control, put it into a kind of remission and then move on to an autologous stem cell transplantation in those patients where we feel that is a safe and reasonable procedure to do. That is still our first line treatment. Now there are some doctors out there who are moving away from autologous stem cell transplantation because the novel agents are really very effective and a maintenance program on the novel agents is something that better fits the patient.

Foss I was just going to ask that question as to how successful we are with treatment and how that has changed over the last 10 years?

Dickinson It has changed enormously. Myeloma is one of the good stories in hematology. In past decades myeloma was difficult to treat and steroids, which is another kind of drug that I have not mentioned, that was always part of our first line treatment and conventional chemotherapy, were really the only tools that we had. Then along came autologous stem cell transplantation, which is where we intensify the chemotherapy dose in patients fit enough for it and that really changed the outcome of myeloma because many patients did need to have ongoing treatment for a couple of years and we saw that the length of time the patients were living without the side effects of multiple myeloma increased after autologous stem cell transplantation came along. Now we have these great new

agents beginning with thalidomide, which of course is an old drug with a new indication and then moving on to Revlimid, lenalidomide, and Velcade, which are highly effective in putting patients into very deep remission and can be given for a long period of time and are used to maintain that remission. One of the big questions we have in myeloma treatment now is whether those new treatments are as good as autologous stem cell transplantation when used frontline and I think that question is unanswered but I think patients who are using those new treatments, Velcade, lenalidomide, thalidomide with or without steroids or chemotherapy in combination, can be very confident that they are likely to experience a good response and to live much, much longer with disease and without symptoms from their disease. The other very important drug is the bisphosphonates. So these injected drugs that we use are usually on a monthly basis, Zometa, Aredia which helps strengthen the bones and prevent those fractures that I mentioned has really changed the quality of life for patients with multiple myeloma.

23:32 into mp3 file <http://yalecancercenter.org/podcasts/2013%200127%20YCC%20Answers%20-%20Dr.%20Dickinson.mp3>

Foss As patients stay on these drugs longer and longer, can you talk a little bit about the side effects, particularly the long term side effects, of these drugs?

Dickinson Beginning with Velcade which is an injected proteasome inhibitor, so it is a biological agent that works differently from chemotherapy, this is a drug which is either given under the skin or given intravenously and at that time many patients will develop peripheral neuropathy as their exposure to the drug increases. Now peripheral neuropathy is where you can have either loss of sensation or painful feeling in the fingertips all the time and sometimes more than that and sometimes you can have neither problem. So there would be difficulty unbuttoning a shirt and that is when the peripheral neuropathy is severe enough for us to want to change treatment. In many patients with multiple myeloma we include steroids such as dexamethasone and prednisone and those drugs cause thinning of the skin, thinning of hair, can worsen diabetes over time and can change body shape, cause weight gain over time so that is something we have to grapple with and often we will reduce the dose of steroids over time once the myeloma is under control. With Lenalidomide or Revlimid, its main problem is low blood counts, and that is probably not so much a cumulative problem, it is something that is dose related and we can often adjust the dose of Revlimid to deal with low blood counts as a consequence of that. Probably after a couple of years of treatment of Revlimid, if that is what is required, many patients won't need a dose reduction because of low blood counts but otherwise it is a relatively well-tolerated drug. Thalidomide is a

little bit more difficult to take for a long period of time. It is probably more likely to cause constipation and gastrointestinal problems. Some patients get a little bit nauseated or feel a bit sleepy on the thalidomide and there is also some contribution potentially to peripheral neuropathy as well with that particular drug. So it is a little bit more difficult to use for a very long period of time, but again it is effective and it is probably effective in patients when lenalidomide has failed. Sometimes going back to thalidomide can be really quite good for myeloma.

Foss Micheal, you and your group at Peter MacCallum have done a tremendous amount of work in the research of some of these new agents and have helped us to make some strides forward in multiple myeloma. Can you talk a little bit about some of the work that you have done and also the new clinical trial that we are doing in collaboration between Yale and Australia?

Dickinson Absolutely, so at Peter MacCallum we have done a lot of work on these groups of drugs that affect the epigenome, and I won't get too bogged down in what that means, but they are biological agents not chemotherapy, and they change the way cancer cells express their genes and seem to lead to death of cancer cells and we have focused on this particular group of drugs for a number of different hematological cancers including multiple myeloma and an example is the histone deacetylase inhibitors which is a particular group of drugs and an example of that drug is a drug such as panobinostat and also another example is romidepsin. Now romidepsin is available in the United States for certain indications, not for multiple myeloma, but at Peter Mac, what we did is we combined romidepsin with Velcade and we found that this particular combination was quite effective in the treatment of multiple myeloma and was able to resensitize patients to Velcade if

27:45 into mp3 file <http://yalecancercenter.org/podcasts/2013%200127%20YCC%20Answers%20-%20Dr.%20Dickinson.mp3> they had been exposed to it before and it had failed after a period of time. We found that romidepsin could resensitize it. Now in this trial what we are doing is we are taking this drug romidepsin and we are combining it with Revlimid. Now we know that Revlimid will work in many, in fact most patients with multiple myeloma, and at some point it will stop working in a proportion of patients and they'll need a different treatment and then somewhere down the track that different treatment may stop working, and we need to start looking at other options. Now for a proportion of those patients, Revlimid will work again and so what we are using is Revlimid as a backbone anti-myeloma treatment and we are adding romidepsin to see whether it will increase the effectiveness of this Revlimid when used in patients who failed other treatments for multiple myeloma. They do not have to have had Revlimid before to go on the study, but what we are trying to do is increase the

response rate and increase the duration of response in multiple myeloma. In particular with this trial, which we have called the RIDS study, we are also looking at the effect of this combination of Revlimid and romidepsin in certain subtypes of lymphoma as well and we are very optimistic that we will see some activity from this combination, it's a very interesting combination.

Dr. Michael Dickinson is a consultant in hematology at the Peter MacCallum Cancer Center in Melbourne, Australia. 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.