

Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. 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. Wilson is joined by Dr. Harriet Kluger. Dr. Kluger is Associate Professor of Medical Oncology and a member of the Yale Cancer Center Melanoma Program. Here is Lynn Wilson.

Wilson Let's start off by having you tell us a little bit about what melanoma is?

Kluger Melanoma is a cancer that arises in the pigmented cells, mostly of the skin, but also other parts of the body. It can also start from the mucosal surfaces inside the mouth, inside the nose, in the perianal or perivaginal area and it can also originate in the eye from the pigmented cells in the eye.

Wilson Tell our listeners about your background and how you became interested in this field, how did you become interested in medical oncology? Tell us about your training, and how it brought you to this point?

Kluger Well it was kind of a long road and a number of personal instances that led me down this path, but I started off working as a general internist after finishing my training and I did that for about three years and then decided that I wanted to be an oncologist. The main reason for that decision at that time was that big discoveries were starting to be made in oncology. When I trained as a medical student in oncology, there really was not very much to offer patients. We could give them chemotherapy, obviously radiation was always an option, but we had very few curative options and I think the main reason was because we did not understand enough about the basic biology. So in the early 90s' a number of big breakthroughs occurred in different malignancies and drugs were developed to target certain changes that happened in cancer cells and those started to lead to improvement in quality of life, duration of life and actually improvements in the cure rates as well. So, I really wanted to be a part of this big change in medical care even if I can only play a small part.

Wilson And how did your interest in melanoma develop?

Kluger For a number of reasons. Firstly, there was a huge unmet need in melanoma. When I finished my training here at Yale in medical oncology,

there were very few people nationally who even focused on this disease, probably around 20 or so. Every time I went to the national meetings, the melanoma hall was empty whereas the breast cancer and prostate cancers halls were all full. So clearly there was a lot to be done. There was also nothing to offer those patients at that time and I

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Wilson I know you are a melanoma expert, but are there other types of malignancies or cancers that you have expertise? Any patients with other types of oncologic diseases that you help?

Kluger I do treat a few patients with breast cancer, and I also treat patients with kidney cancer. The main reason for the kidney cancer is because some of the therapies that we give for melanoma are the same as those that are given for kidney cancer, so even though the disease starts in a completely different organ and the clinical course is very different, these two diseases tend to respond well to immune-based therapies and therefore, disease units are formed around kidney cancer and melanoma together, and that is why we treat both of those cancers together.

Wilson Do we have any understanding about why these types of cancers seem to be responsive to immune-based therapies compared to other types, for example?

Kluger We are starting to understand a lot of things about the cancer cells and how and why they suppress the immune response. The truth is though that there probably are other malignancies that are going to be responsive to immune therapies but historically, immune therapies have been developed against melanoma and renal cell primarily, but as these drugs are further along in development, we are now starting to find, for example, that they sometimes work in ovarian cancer, lung cancer, prostate cancer, and other diseases as well. So the hypothesis that melanoma and kidney cancer are the most immune responsive malignancies is actually just historical.

Wilson I see, are there different kinds of melanoma, different varieties?

Kluger Yes, melanoma as I said can be divided into a number of different subgroups, one way of dividing it is by the origin, or the cell of origin. Melanomas can arise in the skin, those are called cutaneous melanoma. Melanomas that arise in the palms or soles of the skin which are non-sun exposed areas are called acral lentiginous melanomas. You can also get them under the nailbeds. You can have mucosal melanoma that can arise, as I said earlier, either from the mouth, the nose, the anus, or the perivaginal area. Occasionally, we can even see them in the esophagus, and then ocular melanomas arise in the eye. Then among the cutaneous subtypes, there are different varieties as well and that depends on the look, the appearance, and now we are starting to have molecular classifications. So some of the melanomas have mutations in gene A and others have mutations in gene B and we are going to have a whole bunch of new names for these diseases as we move forward.

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Wilson And with that information, does that help you determine a therapeutic course for a patient, a different prognosis for that patient, if they have certain molecular markers or certain types of melanoma?

Kluger Absolutely. The clinical behavior of the different types of melanoma, depending on the site of origin, is very different. For example, if melanoma in the eye does spread, it will tend to spread to the liver, it does not go to the lymph nodes, mainly because there are no lymph nodes that drain the eye. Mucosal melanoma has different patterns of spread from the regular skin melanomas. Just based on the cell of origin, there are differences in prognosis and there are differences in patterns of spread. When you get to the molecular subtypes that we are starting to develop now for example, the melanomas that harbor this mutation in a gene called BRAF will tend to have a worse prognosis if they are not treated with drugs that target the mutated BRAF molecule, so there are prognostic implications there as well as therapeutic implications.

Wilson Who do you think is most at risk for melanoma? Is it people who spent a long time and a lot of time in the sun when they were younger? Are there genetic predispositions? Are there risk factors that can be considered by people so that they can decrease their risk by avoiding sun exposure for example?

Kluger Absolutely, you actually just mentioned the two most common risk factors for melanomas, they are genetics and sun exposure primarily, and it is not just sun, that is all kinds of UV radiation, so that includes tanning parlors. Certainly when it comes to sun exposure that is something that a person can modify. Obviously it is a little difficult for people to change their job or where they live, but if you have a job that entails a lot of outdoor work or live near the equator, dressing properly makes a huge difference. Australians have been best at really trying to modify the behavior of their nationals. There were lots of national ads on TV and in the new papers about not going to the beach in the middle of the day, using sun protection, using sunscreen, using protective clothing, clothes that have SPF-50 when they go down to the beach, cover themselves, not walk around just in bathing suits and Australia is the only country that I know of that has actually succeeded in decreasing the incidence of melanoma. In other countries it is still going up.

Wilson I know that sunscreen, for example, might prevent somebody from getting a sunburn, but does sunscreen actually help to decrease the risk of melanoma?

Kluger It helps to decrease the risk of melanoma, but it does not eliminate it completely. There was a study done in Australia recently where they gave some people sunscreen for free and were told to apply it a couple of times a day and the other people just applied sunscreen as they felt was right,

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and there was decrease in the incidence of melanoma. So certainly it decreases the incidence. It definitely decreases the incidence of basal cell and squamous cell dramatically. It is likely less effective for melanoma, but when we have patients with high risk for melanoma based on the genetics, people who have got red hair, blue eyes, freckly skin, people who are unable to tan, we suggest that they use sunscreen as the last line of defense against the sun. Still try not to go out in the middle of the day, wear broad brimmed hats, not baseball caps, long sleeves, long shorts, and so on and only when they have to be in the sun and only in those areas that are necessary to expose to the sun, should they use sunscreen as the form of protection.

Wilson Do we see epidemiological differences, men more than women, is it different in certain age groups? And what about race, what role does that play in this?

Kluger We see it much more frequently in fair skinned individuals, you do see it in African Americans and in Hispanic people, but it is normally on the palms and the soles, although not always. But certainly much more frequent in fair individuals. It used to be more common in men than in women, but that is starting to change and we are particularly seeing an increase in the incidence in young woman, particularly on the legs. The thought is that that might be because of the use of tanning products. Maybe 20 or 30 years ago men were more exposed because of occupational differences and that is also starting to change.

Wilson How do you make this diagnosis and are there screening programs, is screening effective for this?

Kluger Screening appears to be effective. We do think that when we catch it earlier there is a decrease in the likelihood of developing metastatic disease, although that is still being studied. It certainly increases the number of diagnoses when we screen, so that may be one of the reasons why we are finding more and more but a lot of melanomas are picked up on routine screening exams. In other cases it is because the patient feels that a lesion is tingling, or it is changing color or just looks odd for no good reason. There are a number of criteria that are applied by dermatologists to assess how suspicious a mole is, we call it the ABCDE and there is now an F criterion. So A is for asymmetry, B is for border, so a border that becomes irregular, C for color, so a change in color, D is diameter over 5 mm, E is for evolution or elevation, and F now stands for funny looking.

Wilson So what needs to be done during the screening, are there tests that a patient needs or scans that need to be done, or is it as simple as a full body skin examination?

Kluger It is a five minute full body skin examination. The dermatologists are starting to develop dermatoscopes which are fancy machines to look at changes and big magnifying glasses. They can

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sort of see molecular changes through these dermatoscopes but they have not been FDA approved. They have not been completely proven to be beneficial in early detection. So for now, we are relying primarily on the dermatologists eyes and experience and patient reporting, but all in all it just takes a few minutes.

Wilson Once we have identified somebody with something that we are concerned about or perhaps the patient says hey, I have got this mole, it looks irregular to me, it has changed, I am worried about it, what happens next?

Kluger The most common thing is that the mole gets biopsied. It could be biopsied in a number of different ways depending on the location and how big it is. The biopsy specimen is sent off to the pathology lab and if it is malignant the patient then needs to have what we call a wider excision so that if there are rogue cells that have escaped from the tiny little tumor, those get cut off in the wider excision and that is normally done by a specialized surgeon.

Wilson And is the procedure typically done in the doctor's office as an outpatient of these biopsies?

Kluger The initial biopsy is done in the outpatient setting, the wider excision is typically done in an operating room depending on the depth of the melanoma, how deep it has invaded into the skin. We sometimes take a few lymph nodes to see if melanoma cells have spread to the lymph nodes as well and when that is done it requires full anesthesia.

Wilson So once we have this diagnosis, what are some of the treatment options that run through your mind for a patient?

Kluger It depends on whether the melanoma spread or not, primarily. Melanoma that is localized just on the skin, we simply excise it and we do not need to do anything further. If it is a very deep melanoma, we will look at the lymph nodes. If the lymph nodes are negative, sometimes we will do a CAT scan or chest x-ray just to make sure that nothing has spread and we may do imaging periodically, as we follow the patient. If a melanoma has spread to the lymph nodes it is somewhat controversial as to whether we should give immunotherapy to kind of increase the likelihood that any rogue cells that got to other lymphatic nodes that have not been removed get treated and if it has spread to other organs where it is caught either by CAT scan or because the patient has symptoms, then we do have to give therapy in an oncologists office.

Wilson We are going to take a short break for medical minute. Please stay tuned to learn more information about melanoma with Dr. Harriet Kluger.

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Medical

Minute Breast cancer is the most common cancer in women. In Connecticut alone approximately 3000 women will be diagnosed with breast cancer this year, but there is new hope. Earlier detection, non-invasive treatments, and novel therapies provide more options for patients to fight breast cancer. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with the disease. With screening, early detection and a healthy lifestyle breast cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center to make innovative new treatments available to patients. A potential breakthrough in treating chemotherapy resistant breast cancer is now being studied at Yale combining BSI-101 a PARP inhibitor with the chemotherapy drug irinotecan. This has been a medical minute brought to you as a public service by the Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson, and I am joined by my guest Dr. Harriet Kluger and we are discussing melanoma. Harriet, we just talked a little bit about therapy, especially for patients with localized melanoma. Can you tell us a little bit about the possibility of melanoma spreading somewhere else, what are some of the things we get concerned about, detection of that, how do you manage that?

Kluger That is a complex question, typically patients who have had melanoma excised get followed afterwards and sometimes we scan them to look for metastasis, and when we do that, we think that we actually improve outcome. Sometimes we detect the metastasis when someone has symptoms. So the way these metastases are detected really depends on where they are and how big they are and the treatment is also determined by that as well. If the patient, for example, has a primary melanoma from the skin or even a skin and lymph node removed and then 10 years later we have a single metastasis in the lung or the liver or another place, we may sometimes either remove it surgically or depending on where it is, we can even radiate it. Sometimes the patients then do well for a long period of time after that. If there are two metastases, we can also consider doing that but once there are more than two, we have to do what we call systemic therapy which means therapy that goes to all parts of the body. We have two major types of systemic therapies, actually I should say three, one would be chemotherapy, which is what we have used over the years and that is sort of nonspecific, non-discriminant therapy. It does work in a small subset of patients and the problem is that the duration of tumor shrinkage isn't all that long, so it does not work forever. Then we have immune based

therapies in which we have to rev up the immune system to attack

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the melanoma. Then we have a third class of therapies called molecular targeted therapies where we target molecules within the melanoma cell. When I spoke earlier about these mutations we can sometimes drug those mutations and turn off the whole cancer cell machinery a little bit.

Wilson Can you talk to the listeners a little bit more about fundamentally how some of the immune based therapies actually work, what is it doing to our bodies to try to fight these cells?

Kluger Most of the immune therapies rev up the immune system in a variety of ways so, for example, you can rev up T-cells with the drug called Interleukin-2 which has actually been around for a couple of decades. There is a subset of melanoma patients who respond very well to that and some have even seen cure. There were patient's treated in the early 1990s with high dose Interleukin-2 who have not had a recurrence. It almost fools the body into thinking that it has a really bad case of the flu and people feel like they have got a bad case of the flu and then the immune system will attack the melanoma cells. In recent years, we have gotten a little smarter at manipulating the immune system. There was a drug called ipilimumab, the trade name is Yervoy, that was just approved by the FDA in March 2011 for treatment of metastatic melanoma and this was based on very clever science. Basically a molecule called CTLA-4 was shown to put the brake on T-cells and if you inhibit the CTLA-4 molecule you can have a continuous response of T-cells, so you fool the T-cells into thinking that there is a bacteria around all the time and they remain activated. So, they are sometimes in the nonspecific fashion and they can become active against the cancer cells. The problem with this approach is that we also get what we call autoimmune disease. The immune system can start attacking parts of one's own body and people can get diarrhea and hormone problems and things like that so those can be difficult to manage, but certainly if you weigh what we call the risk-benefit ratio, in other words, the benefit of the treatment versus the risk of getting one of the side effects, the risk-benefit ratio certainly favors trying this treatment in patient's with melanoma that spreads.

Wilson And does it seem to be equally favorable regardless of the molecular profile of an individuals problem?

Kluger That's what we think so far, but the jury is still out on that. We are also trying to modify this approach. There is a new target that is being tested in the clinic called PD-1 which is also found on T-cells. It is also one of the brakes on T-cell longevity and activity, an antibody that blocks that molecule is being used now. We have used it for a couple of years and were seeing good responses there too. We are starting to combine drugs, we are starting to combine these drugs with radiation. So, for example, if you use ipilimumab or the CTLA-4 blocking drug together with radiation, when you radiate you have the melanoma cells start to secrete proteins into the blood

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system and some of these proteins are specific for the melanoma cells so it can only synthesize the immune system even further to attacking the melanoma cells. So, lots of different modifications are ongoing of this approach. This is really a new paradigm in cancer therapy and other diseases. We will also be starting to study it in other disease such as lung cancer in particular, and obviously kidney cancer as well.

Wilson That is fascinating. When you are faced with the dilemma of the patient who has had metastases of their melanoma, are certain sites of the body more difficult to treat than others?

Kluger Yes, not all sites are equal, sometimes the melanoma can metastasize just in the skin and those are relatively easy for us to treat. Sometimes we can treat it with cream only, immune stimulating cream, basically. If it goes to lymph nodes sometimes we can resect it whether it is in lymph nodes or lungs or certain locations. I would say that the brain is a slightly unique location in that there are two problems there. Firstly, if the tumor grows from the small size, depending on where it is in the brain, it can cause symptoms so we do not have a lot of wiggle room there. The other problem is that sometimes drugs do not get into the brain whereas they might get into other sites of the body. So over the years it was considered a difficult site to treat but there too we have made a lot of progress in recent years, improved imaging, particularly MRI scans enable us to find these brain metastasis when they are really small and not causing any symptoms, and reduced high doses of radiation called gamma knife therapy or stereotactic radiotherapy where we can actually cherry-pick at these tiny little brain metastases and treat them when they are very small and often times patients do very well for a long time and it is not the brain metastases that become a problem.

Wilson We hear the term multidisciplinary approach for patients with cancer and other diseases. Tell our listeners what that is and why it is important?

Kluger When patients have cancers, particularly metastatic cancers, sometimes it is a little bit of dilemma of how to approach these patients. Should we start off with the systematic therapy, should we radiate first to get antigen releases, or as I mentioned before, should we do surgery? Sometimes we have to use more than one approach in combination so we have a multidisciplinary team of people focused on melanoma. This includes pathologists who might be able to help us determine whether it is one kind of melanoma versus another, sometimes we do not know what the origin of the melanoma was and they help us understand the mutation and helps us with determining systematic therapy based on these mutations. We have radiologists who specialize in melanoma and can often tell us if something looks like a melanoma metastases versus a new lung cancer. We have surgeons who focus on this disease as well as radiation therapists and medical oncologists. Now that patients with metastatic melanoma are living longer, we have also started to incorporate neurosurgeon and neuro-radiation therapists who help us control the brain metastases. So the good

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news is we have choices now, multiple different approaches that can be used and there is no good script for how to treat a patient. Every patient is individual and the decision tree has to be very individualized, so we have a group that gets together at least once a week, and we also often work together in clinic, and we sometimes see patients together at the same time in order to make these decisions in the multidisciplinary fashion and this is a wonderful luxury to have here.

Wilson Let us get back to therapy just for a second, obviously the targeted therapies are some of the newer therapies, the immuno or immunomodulating treatments have been around for a longer amount of time. Do you suspect that these targeted type therapies are going to make big advances say in the next 5 years or so?

Kluger Yes, absolutely they have. I assume you are talking about the molecular targeted therapies so the therapies that target the melanoma cell rather than the immune system.

Wilson Yes.

Kluger So one of those was just approved last summer, a drug called vemurafenib and this is a pill, it is a drug that targets the mutant BRAF in those melanomas that have the BRAF mutation and approximately half of metastatic melanomas can be treated with this drug. So that was just approved. Glaxo-SmithKline is developing a drug that will probably get approved as well in the next year. We are now starting to study combinations of the BRAF inhibitor with other inhibitors to increase the time of the patient's response to therapy and we are also studying combinations with inhibitors of different pathways so that we can overcome some of the escape mechanisms that these cancer cells ultimately develop when they are treated with a targeted therapy and the studies combining the targeted immune therapies with the targeted molecular therapies, so that is going to be interesting as well and overall there is a lot going on in this field, it is very busy.

Wilson It sounds like it. You had mentioned some of the benefits, you described the multidisciplinary care team. What else can you tell us about the melanoma program at Yale?

Kluger We have a lot of research ongoing starting from basic science all the way through clinical research. It is a fairly big group, Dr. Ruth Halaban is the basic scientist who was recently awarded a grant from the National Cancer Institute to study melanoma specifically and she is running a lot of genetic studies and discovering new mutations in the melanoma cells. There is an immune program that is a component of that, there is an epidemiology program and so on, so this grant actually brings in a lot of activity and it enables us to study patient's samples and ultimately some of that information is taken back to the clinic directly. So because we have this grant we can

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sequence patient's genes within the cancer cells to see if they have mutations and sometimes that helps us to determine what approach to take and there are lots of other research programs as well, particularly the clinical research program, it is a fairly big operation and we have a number of ongoing clinical trials. We are going to have a surgical trial opening up soon as well, and hopefully, also trials specific for patients who have got brain metastases.

Wilson If a patient thinks they have a problem and they have a mole that

they are concerned about, what would be the best way for them to get screened or at least get that lesion evaluated, what would you recommend?

Kluger It is typically a dermatologist, but depending on the patient's insurance it is not always possible to go directly to the dermatologists but most of these moles can be biopsied by a primary care physician as well, except anything on the eyelid, on the face, or a place where you worry about scarring, but for the most part the biopsy is the easiest part and a lot of moles are biopsied that they are not melanoma, I cannot tell you the percentage on that, but by far the vast majority are benign.

Dr. Harriet Kluger is an associate professor of medical oncology and the member of the Yale Cancer Center Melanoma Program. 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.