Yale CANCER CENTER answers

WNPR Connecticut Public Radio

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Melanoma Awareness 2015

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Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you could submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week, it is a conversation about the management of melanoma with doctors Dale Han and Jennifer Choi. Dr. Han is Assistant Professor of Surgical Oncology at Yale School of Medicine and Dr. Choi is Assistant Professor of Dermatology and Director of The Yale Onco-dermatology Clinic. Here is Dr. Anees Chagpar.

Chagpar Dale, I want to talk first with you. So people will present, especially during summertime I would anticipate, with moles and things to their dermatologists. Take me through the process of how they get to you.

Han That is a very good question and people often wonder what the process behind this is. Oftentimes patients will do their own examinations, find a lesion that they have never seen before or that looks suspicious, and then bring it to the attention of a primary care physician, or if they are seeing a dermatologist already, to their dermatologist. This lesion is then evaluated and oftentimes a biopsy is then obtained and if that biopsy comes back with a pathology showing melanoma, the patient is usually then referred to a surgeon, preferably a surgical oncologist who is experienced in the management of melanoma, and then the treatment options are discussed at that point.

Chagpar Jennifer, tell was a little bit more about treatment options, is this chemo first, is this radiation, is this surgery, how does all that work?

Choi The first treatment for melanoma is a wide local excision and then at that point, it depends on what you call Breslow depth of the melanoma which is how deep a melanoma is; it is measured in millimeters and thin is less than 1 mm and so if it is less than a millimeter, then it is a wide local excision and that is pretty much all that is needed with very close follow-up with your dermatologist. If it is over a millimeter, then at that point, the surgical oncologist will discuss with you the need or the recommendation to do something called a sentinel lymph node biopsy and then it depends on those results. If that is positive, then they will do something called staging with a CAT scan and if there is any evidence of organ involvement, that point is when chemotherapy comes in.

Chagpar Dale, you are one of the first ones to see these patients. How do you determine what exactly is a sentinel node biopsy? When do people need it? And what happens with the results?

Han Staging of patients is one of the critical things that we think about for prognosis and treatment options. So the theory and hypothesis behind the development of this technique was that if a melanoma had some cells that spread to the draining lymph nodes, which is oftentimes the first place that melanomas will spread to, this is a technique to check that. Because the vast majority of

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patients with melanoma present with what we call localized disease, meaning there is no evidence of disease in the lymph nodes or anywhere else in the body, that is about 85% of patients with

melanomas, and for most patients, as I mentioned, when you first see them, you will examine the primary lesion and also examine the adjoining lymph node basins, and as I mentioned, most of these patients would not have any enlargement in their lymph nodes, so you are really trying to determine if there is microscopic spread from the melanoma to these draining lymph nodes. This procedure essentially uses a radiotracer, a blue dye that is injected around the melanoma site and uses that to trace out the lymphatic drainage to the draining lymph node basins and there is a way that you can track the first lymph node which is considered the sentinel lymph node and would be the first to essentially drain the skin area with melanoma and potentially first harbor any spread of that melanoma and we can find that lymph node, make a separate incision, remove it and send it to the pathologist who then has the job of looking for any microscopic deposits of melanoma in there. We generally recommend sentinel lymph node biopsy for melanomas based on their Breslow thickness and the studies that have been done and there have been extensive studies, primarily the Multicenter Selective Lymphadenectomy Trial 1 which would demonstrate that this procedure should be recommended to patients who have melanomas with a Breslow thickness between 1 and 4 mm. Many patients who have thicker melanomas are also candidates for a sentinel lymph node biopsy and the real controversies about patients who have thin melanomas are melanomas that are under 1 mm.

Chagpar Is the controversy because they are so thin that they are likely not going to have any cancer in their lymph nodes?

Han That is absolutely one point, and the prognostic significance of the sentinel lymph node status for patients in that subgroup is debated. So generally, many of us who treat melanoma patients across the country will utilize a 5% risk threshold for this procedure. So that 5% risk threshold usually starts to occur when melanomas are about 0.75 to 0.76 mm in thickness, also if they are ulcerated or have a high mitotic rate. Oftentimes we use these in combination to stratify the patients into risk categories and to see which patients with the melanomas should be offered a sentinel lymph node biopsy.

Chagpar Many patients who may be listening and who may have had breast cancer may be familiar with the term sentinel lymph node biopsy, but in breast cancer, we know that the sentinel lymph nodes are underneath your armpit, but when you get melanoma, you can get melanoma anywhere on your body. How do you know where that basin is? Do you do a special kind of scan before you take them to surgery to see where that drainage goes or do you just get into the operating room and use a gamma probe in all of the potential basins, and prepare to look for lymph nodes wherever they may be?

Han That is a very good question. Oftentimes, I tell patients that surgery for melanoma is doing acrobatics because you can get a melanoma anywhere pretty much on your body, but to answer your question to find where the draining lymph node basins are, we often use something called

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lymphoscintigraphy and what that involves is an injection of a radiotracer around the primary tumor site and then pictures are taken essentially looking for where the radiotracer drains. Oftentimes, we can intuitively determine where the melanoma will likely drain to, but the lymphoscintigraphy is a great way to confirm that and also to determine if there are aberrant areas where the melanoma may drain into.

Chagpar And so you go after those lymph nodes, you take them out and then does the pathologist look at them right there during the surgery?

Han It is a little controversial but most of the surgeons who treat melanoma in this country, the surgical oncologists, do not do what you are alluding to which is a frozen section, they actually do this on permanent pathology and one of the primary reasons is that the foci of melanoma that is often found within the sentinel lymph node is microscopic and sometimes can only be found on one slide. If that slide is used for a frozen section and if there is an issue, then you may have lost that potential diagnosis.

Chagpar So they have their surgery and they go home and then they come back to the clinic and now they have got a sentinel node that does have cancer in that lymph node, do those patients then need more surgery, do they need chemotherapy, do they need radiation, what happens next?

Choi If they have a positive sentinel lymph node, Dr. Han can talk more about this, but then there is this question of if they need what you call completion lymphadenectomy and that would be discussed with the surgical oncologist, but after that point, we were talking about staging and doing a CT, so if the staging CT does not show any further involvement, then the medical oncologist will speak to the patient about possibly doing something called adjuvant therapy and adjuvant just means possible chemotherapy that is used afterwards to try to decrease your risk of developing further lymph nodes or further metastasis in other organs.

Chagpar So the first step after you get back the sentinel lymph node is the decision about whether you complete this node dissection, right, Dr. Han?

Han Absolutely.

Chagpar And how are you going to make that decision?

Han At this point, the SSO, ASCO and NCCN guidelines recommend that every patient with a positive sentinel lymph node should be recommended for a completion lymphadenectomy.

Chagpar Even if it is only a single cell?

Han Absolutely, because there have been studies that have shown that even isolated tumor deposits can have a prognostic significance and we do not have enough data right now to suggest otherwise.

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There is a trial ongoing right now and actually the accrual has finished and the results will probably be available in about three or four years or so, called the Multicenter Selective Lymphadenectomy Trial 2 in which they tried to assess whether or not every positive sentinel lymph node patient required a completion lymphadenectomy. Unfortunately, until we get the results of that trial, we will not have any recommendations to tell us otherwise other than that every positive sentinel node patient should have a completion lymphadenectomy.

Chagpar I am going to take off the moderator hat and put on the breast surgeon hat just for our listeners, this is very different than in breast cancer because in breast cancer a single isolated tumor cell really makes

no difference to prognosis and this goes to tell you that breast cancer and melanoma, different kinds of cancers, are very different.

Han Absolutely, there are different biologies of cancers.

Chagpar Let's suppose that you go in and complete the dissection, does the number of lymph nodes make a difference to you Jennifer in deciding whether or not people need adjuvant therapy or are you also of the mindset that one cell could buy you adjuvant chemotherapy if your other staging work up is negative?

Choi Usually it is determined not necessarily on the number of nodes, so if you have any positive node and the rest of your staging is negative, it is still really a case by case basis, they will speak with you to determine other risk factors, but it really will be a discussion of if you need adjuvant therapy even if it's just a single node, so any positivity, they will talk to you about it and also it depends on your age and that kind of thing if you would tolerate it too.

Chagpar Jennifer mentioned that the staging studies happen after the surgery, but do you ever do staging studies before you do the surgery to see if they have got metastatic disease? Is there a benefit to surgery in people who have widely metastatic disease?

Han It is interesting that you brought up that question. It is a bit of a controversial area in terms of your first question of whether or not you need imaging studies and a staging work-up such as CAT scans and PET scans prior to doing any kind of surgical intervention. I will answer the first question, and generally in patients who present who are clinically node negative, meaning that you do not feel any lymph nodes that are enlarged and there is no suspicion based on history and physical or anything otherwise that the patient may have distant metastatic disease or deposits of melanoma elsewhere in the body, generally it is not recommended that you need staging studies beforehand; however, if the patient is found to have a positive sentinel lymph node as we were discussing before, that tells you that this melanoma has a different biology. It is a more aggressive melanoma that tends to spread and that is an indication actually for staging studies to make sure, because those patients are at higher risk now, for distant spread of their melanoma, so in terms of your second question about are there indications for doing surgery on patients with widely

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metastatic disease, that is an evolving field and it is a really exciting time in the treatment of melanoma because since 2011 we now have six new FDA approved drugs which have really changed the field of treatment of patients with distant metastatic disease.

Chagpar We are going to pick up on what those exciting new advances in the treatment of metastatic melanoma are right after we take a short break for a medical minute. Please stay tuned to learn about melanoma management with my guests, Dr. Dale Han and Dr. Jennifer Choi.

Medical Minute *Smoking can be a very strong habit that involves the potent drug nicotine and there are many obstacles to face when quitting smoking, but smoking cessation is a very important lifestyle change especially for patients undergoing cancer treatment. Quitting smoking has been shown to positively impact response to*

treatments and decrease the likelihood that the patients will develop second malignancies. Smoking cessation programs are currently being offered at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven. The smoking cessation service at Smilow operates on the principles of the US Public Health Service Clinical Practice Guidelines. All treatment components are evidenced based and therefore all patients are treated with FDA approved first line medications and smoking cessation counseling. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. For more information, go to yalecancercenter.org. You are listening to WNPR, Connecticut's Public Media Source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my guests Dr. Dale Han and Dr. Jennifer Choi. We are talking about the management of metastatic melanoma. Right before the break, Dale you were saying that this is a really exciting time in melanoma management because there are so many options for how to deal with widely metastatic disease. Jennifer, that usually is the purview of the medical oncologist, so tell me more about what is on the horizon, what do we have, what makes this such an exciting time?

Choi There are several advances, one of them is the genetic sequencing of melanoma, so we now know that 50-60% of melanomas actually carry a mutation in something called BRAF and if we find that a melanoma has a BRAF mutation, then one of the options now is something called a BRAF inhibitor. We have something called vemurafenib and dabrafenib and these have only been available for the last couple of years, and so now if we see a patient with metastatic disease and they have a BRAF mutation, we can use this medication to rapidly help to decrease a lot of the tumors that they have. The only problem with this medication is that within 6 to 12 months a lot of the patients, the majority of them, will actually develop resistance, so then those tumors that have shrunk will start to grow again and so another really exciting thing are what we call two categories of immunotherapies, so one of them is called ipilimumab which is anti-CTLA-4, cytotoxic t lymphocyte-associated antigen 4, and there are two new agents called anti-PD1 program cell death receptor 1 inhibitors and these include pembrolizumab which was FDA approved in September of

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this past year, 2014, and nivolumab which was just FDA approved in December 2014. The way these immunotherapies work is that it does not depend on the patient's mutation status. You can actually use this on anybody with metastatic melanoma and the way it works is that our bodies naturally have what you call a check point inhibition, so when you develop an immune response, CTLA-4 and program cell death receptor, they will act to decrease your immune response so that your body does not go crazy. It is a way to keep homeostasis, a balance, it's checks and balances; however, because of that, the tumors then can bypass these check points and then they can start to grow, so by getting these inhibitors that allow your immune system to be activated, it will then allow your immune system to target these melanoma cells and so because of the advances of these medications, we now are seeing patients with metastases and some of them are achieving remarkable responses and even complete remission with some of these medications.

Chagpar This is something that you hear about on the news and on TV about harnessing your body's immune system because I think a lot of people always wondered, you get an infection, you get a cold, your body fights it off. Your body fights off a lot of stuff, how come your body does not fight off cancer? Dale, I want to come back, however, to this whole idea that if you have got widely metastatic

disease, harnessing your immune system to fight off cancer wherever it may be is going to be useful, or targeting these therapies at the melanoma is going to be useful, but where does surgery fit in there?

Han In the past surgery had a very limited role for patients who had widely metastatic disease and it is about risks and benefits. If you were to surgically try to remove every lesion, it would probably not be possible in patients who have widely metastatic disease. The other thing is even if we try to take out several lesions, you will not affect the patient's survival because there are other lesions that would continue to grow, so surgery had a very limited role and was specific to patients who may have limited disease, good responses to therapy, long progression free survivals where they had lesions that either stayed stable or completely regressed and there were one or two target lesions you could go for. The field does completely change and in fact it is almost on a weekly basis where you have to keep up with things because there are new advances coming in, particularly as Jennifer was talking about, trying to overcome resistance to single-agent therapy and really the horizon now is about multimodal therapy, combining different therapies, whether it is immunotherapy or targeted therapy and trying to use them and the reason why I mention all this is that whereas before you would be very selective about patients that you may surgically remove metastatic lesions, now you have these powerful therapies that are allowing patients who have widely metastatic lesions to have many of these lesions regress and maybe only one or two target lesions are now evident and these patients who would not have been surgical candidates are now surgical candidates. In addition, patients who may continue to have widely metastatic disease, disease that has regressed but stayed stable and there may be just one lesion that continues to grow, those patients may all end up going on to surgery also to remove that resistant lesion or to be able to consolidate the disease.

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Chagpar It sounds like surgery has a role in debulking or taking out what is residual, but it sounds like the real advances, no offense to the surgeons in the room, is really in medical oncology, so tell us about the side effects of these immunotherapies. Is this the stuff that makes you lose your hair and makes you get sick because everybody who comes in who asks about chemotherapy, that is their number one concern.

Choi That is a good question. These medications actually all have their own sets of side effects, so if you look at BRAF inhibitors, it is actually pretty well tolerated. There is a wide range of cutaneous skin side effects that you can actually see from BRAF inhibitors, one of them includes wart like lesions. These are benign. They sort of look like the small rough papules that can occur anywhere on the skin. These are easily treated just by something called cryotherapy or liquid nitrogen to freeze them off. One of the more concerning side effects is something called squamous cell cutaneous skin cancer that can occur due to the melanoma treatment.

Chagpar So you are going to give me a treatment to get rid of my cancer that has a side effect of giving me cancer?

Choi Yes, but the way to think about it is that it is really targeting your melanoma and one of the side effects could be a different type of skin cancer which is very treatable in terms of just getting it off the skin.

Chagpar Got it.

Choi This other type of skin cancer is really not considered dangerous. There have been no reports of metastasis from the squamous cell developed by BRAF inhibitors, so this is just something that, especially if you have had a lot of sun exposure, then in a sun exposed area, you may develop something called a squamous cell skin cancer, but this is again very treatable and then other side effects can include rough skin that is really dry that can become very itchy, we can deal with that sometimes with topical steroids and then in addition, in a small percentage of patients on BRAF inhibitors, you can develop something called hand-foot-skin reaction and this is when your hands and your feet can become very painful and develop very thick callous like lesions that can actually make working with your hands or walking difficult.

Chagpar Forever?

Choi Not forever, there are things that we can use to try to decrease the side effects of this and then also if for whatever reason you stop the BRAF inhibitor, then pretty quickly it actually goes away and then when you talk about the immunotherapies, these are a different set of side effects that we see, so ipilimumab, we should mention that in the patients who are being treated with this, only 10-15% will actually respond, but in those 10-15%, it is a durable response, so these are the patients that if you do respond, you can have a really great effect for many years, but it is associated with several side effects. Some of that includes skin side effects like a dermatitis, again it is usually

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tolerable and we can treat it with topical steroids. The other more concerning side effects include colitis, people can get really severe diarrhea, and hepatitis which is the inflammation of your liver. In addition, there are endocrine abnormalities such as inflammation of your thyroid and also of your adrenal glands and sometimes of your pituitary gland, so all of these are possible side effects that we see that sometimes if they are severe enough, you have to hold the treatment and then sometimes give systemic steroids to deal with it. With the anti-PD1 therapies, we are still collecting a lot of data, you can still see some of the colitis and hepatitis and also even dermatitis and different types of rash. In general though, it does seem less severe than ipilimumab, so it is generally pretty well tolerated as a whole in terms of a class of drug.

Chagpar With none of those did I hear that your hair falls out.

Choi So not really, hair loss is not a huge side effect of any of these.

Chagpar I am sure that there are a lot of patients out there right now who are jumping up and down for joy. Dale, I want to ask you, one of the things that Jennifer mentioned is targeted therapy, looking for genetic mutations in BRAF and this kind of thing, so is every single melanoma that you take out genetically sequenced so that we know what mutation it has or it does not have?

Han We do not sequence every single melanoma that we take out but we do look for specific mutations and mutations such as BRAF which are driver mutations and are druggable targets in which we have therapy available, yes we do test for those specifically. We often times test for BRAF, NRAS and so forth but to test every single melanoma at this point, we do not do.

Chagpar So if the melanoma has a BRAF mutation, they would get a BRAF inhibitor and the immunotherapy seemed to work for just about everybody, is that right, Jennifer?

Choi No, not necessarily. Like I was saying, with ipilimumab, you will only see response in 10-15% of patients, so it does not work in everybody, unfortunately, and then the anti-PD1 inhibitors, pembrolizumab and nivolumab, these we are seeing approximately a 30-35% response rate, so again it is not in everybody.

Chagpar How do you know when you are going to use an immunotherapy and if you are not going to use an immunotherapy, then what, what do they get?

Choi As Dale was mentioning, this is a rapidly evolving field. Literally melanoma is one of those fields that is changing by the week, but right now, given just the recent introduction of these anti-PD1 inhibitors, the guidelines suggest that if you have a BRAF inhibitor, you have to look at the patients performance status, so even though they have metastasis if they are actually doing quite well and they are not rapidly getting ill or worse, then people are considering starting immunotherapy first. If they do have a BRAF mutation and they are rapidly decompensating, they are not doing well and it is growing rapidly, then you will give a BRAF inhibitor first so that you

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can control the tumors and then probably eventually also then start an immunotherapy, so immunotherapy really is becoming like a first line treatment now and right now, there are a ton of studies in terms of what is better, ipilimumab, pembrolizumab or nivolumab, do we do a combination, do we give a BRAF inhibitor first and then do immunotherapy, or vice versa, so there are multiple studies that are trying to determine what really should be first line.

Chagpar And what about if patients do not have a BRAF mutation? What do they get?

Choi If they do not have a BRAF mutation, then immunotherapy is now considered first line.

Chagpar First line.

Choi Yes, they are going straight to it.

Chagpar In this rapidly evolving field of melanoma therapy, Jennifer mentioned a lot of clinical studies and I know that clinical trials are really important, there are a lot of them going on at Yale and elsewhere and they really do push the field forward in terms of finding out what is the better therapy and so on, do you find that your patients are enthusiastic about participating in clinical trials or is there still some trepidation about being on these trials?

Han In general, I would say many of our patient are very enthusiastic about being enrolled in clinical trials. You have to remember that prior to 2011, they really were not that many good options for patients with metastatic melanoma yet, you had high dose IL-2, you had adopted cell therapy, but really the options were not nearly as robust as they are now and with all this excitement, with all these new therapies, I think the patients have also adopted that enthusiasm and it is critically important because although we have these new drugs that are FDA approved, we do not know how to

combine them appropriately yet to be able to maximize outcomes for patients.

Dr. Dale Han is Assistant Professor of Surgical Oncology at Yale School of Medicine and Dr. Jennifer Choi is Assistant Professor of Dermatology and Director of the Yale Onco-dermatology Clinic. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.