

Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at Yale Cancer Center. 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 can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about clinical trials for colon cancer with Dr. Howard Hochster. Dr. Hochster is Professor of Medicine in Medical Oncology at Yale School of Medicine. Here is Anees Chagpar.

Chagpar Howard, why don't you start off by telling us a little bit about colon cancer? What do we know about what makes it tick and how we are trying to get around this problem of colon cancer through clinical trials?

Hochster How many hours do I have?

Chagpar You have half an hour, go.

Hochster This is obviously a very large topic, but we do know a lot about colon cancer transition from polyps to becoming malignant and there are a number of very specific changes in the cellular instruction manual, the DNA of the cell, that happen along this pathway that are very well described. These are sometimes called the drivers of the cancer or their mutations that instead of being a normal check and balance on cell growth become either lost or broken or some way un-operable so that the cells grow out of control and there are multiple things that happen along the way from the time that a normal lining cell of the colon, which is called normal epithelium, turns into a bunch of abnormally arranged cells, which you call a benign polyp, to becoming a malignant invasive cancer where it can grow, spread and eventually cause the death of the host. These are well described gene modifications. This all comes out of our remarkable knowledge in molecular biology that has been accumulated over the last twenty years. So the exciting news is now we are learning some important lessons about this molecular biology that gives us treatments in the clinic.

Gore It sounds like we know so much about all these gene mutations. Why can't we just turn them all off, why are people still dying of colon cancer?

Hochster First of all, these things tend to happen probably 10 years or

so before it shows up, so we really have a big problem in knowing when this is happening in a susceptible individual, or people who are healthy, and the second thing is that some of these changes are not very susceptible to our current ways of using medications to block them. Some are, and those are giving us some of these new treatments, but some are what are called undrugable mutations. We just have not figured out a way to turn off these improper signaling pathways.

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Gore Does everybody's colon cancer have the same sequence of abnormal genetic events?

Hochster Well the sequence is probably not the same, but there is a kind of least common denominator pathway that has about half a dozen changes that we know are very very common in most colon cancers.

Chagpar Howard, let me get this straight, are these mutations in the tumor itself or are these genes that you can screen normal people for and tell them that they are at an increased risk of getting colon cancer?

Hochster In general, they are not genetic changes. They are not things that people are passing down to their children and they are not inherited or heritable traits. In general, they are changes in those cells that wind up becoming cancers. So when we look for these genetic profiling changes we take the tumor tissue and we look and see where the bad genes are, but there is one well described situation called Lynch syndrome where there is an inherited deficiency and something called mismatch repair enzymes that runs in families and that can contribute to this. An interesting thing with these Lynch syndrome families is they tend to have a much higher chance of developing colon cancer, but it is a usually early stage colon cancer, it does not spread. Their biology is very different.

Gore Is it standard now, when I have my 50-year-old colonoscopy and they find a polyp or God forbid a cancer, is it if I go anywhere are these genes going to be studied automatically? Is that a standard diagnostic assessment?

Hochster No, not really, because we would not know what to do with it anyway, most of the time, nearly 100% of the time, when these kinds of polyps,

benign adenomas, tubular adenomas and such kinds of benign polyps are removed, that is the treatment. You do not need to do anything else. But if they are left in place over three to five years they can become malignant. In certain people it can be much faster, I see people where they have had a colonoscopy one year and the next year they have cancer and that is faster then we think it happens in most people but we cannot be sure that everybody has the same time course.

Chagpar Getting back to screening with these genetic profiles, when you were talking about Lynch syndrome, who gets that? Should everybody be tested for this mismatch repair of genes or are there certain people who are at increased risk who should be tested? How does that work?

Hochster Normally, we can define Lynch syndrome, besides the biochemical changes by the familial history and that would include a first-degree relative who has colon cancer at a young age and two subsequent generations. So, if that fits your family history, it is something to see a genetic counselor about. But, usually, if we find a colon cancer in a young person, we take their history when we sit down with them and we say, oh, their mother, their father, their brother and sister or

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somebody else in the family who is a first-degree relative or a close relative also had colon cancer, particularly at a young age, and that kind of sets off alarm bells and then we would get the genetic testing.

Chagpar And so the people who get that genetic testing, let us suppose I test positive for a Lynch syndrome, does that mean that in my cancer, you said that we also test for certain genetic mutations in cancers themselves, does that mean that I will have a certain genetic profile that people who are not Lynch carriers would not have?

Hochster The question is, do other people who do not have Lynch syndrome, can they get these same changes.

Chagpar Yeah.

Hochster Rarely, some people get it sporadically and some people have it through a different mechanism that is not inherited where the gene kind of is turned off or silenced. But those are the unusual cases. Most of the time when we find this biochemical situation of the mismatch repair enzyme deficiency or sometimes it is called microsatellite instability, then that is most of the time associated with a Lynch family.

Gore You said that some of these mutations are treatable with medications now. Is this getting rid of the need for surgery for colon cancer? If I have an early cancer, can I be treated with one of these magic medicines and not have to have partial colectomy?

Hochster That would be our eventual goal, but we are not really there yet. So where we are is that we are starting to see in a number of cancers molecularly driven treatments. So, basically when we find a specific gene abnormality in a particular patient, there may be drugs that turn off that signal. The best one you are familiar with is people who develop the BCR-ABL translocation for CML, for chronic myelogenous leukemia, and you can give them this drug imatinib that turns off the signaling. We have a medication like that that works in melanoma for people who have a certain mutation in a protein called BRAF. So, there is a drug that turns that off for melanoma and in colon cancer now we are doing trials and the drug did not work as well for colon cancer as it did for melanoma, but we know now by combining it with another drug that works on the same pathway a little up higher up the chain that it seems to be working quite well. So we are doing a trial now that just opened for BRAF mutated colon cancer where we are combining one of these RAF-inhibitors with an EGFR inhibitor, that is an antibody called cetuximab, and then an AKT inhibitor, which is another investigational drug similar pathway, but I think the important thing for people to know is that if they have colon cancer and they are getting chemotherapy there may be more specific medications available if they have certain gene mutations. There are two main gene mutations that are applicable to metastatic or advanced colon cancer today. One is this

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BRAF gene and that is about 8% of all colon cancer and the other is a gene called KRAS. If you have a KRAS mutation, unfortunately we do not have a treatment for that, but it tells you that these other drugs won't work, these anti-EGF drugs would not work so that is kind of a personalized medicine in a negative way, as in, do not waste your time on a drug that is not going to help you, but the people who have these BRAF mutations, we are developing drugs

and we now have a very exciting trial going on. If there are people out there who have metastatic colon cancer, it is important for them to speak to their physician about getting these tests done.

Gore That is really fascinating, for our listening audience, I think people may be a little uncertain in terms of how this whole thing works with colon cancer and they are the ones hopefully getting their screening colonoscopy. Could you outline who gets surgery, who gets chemo, who are the candidates for clinical trials? I think this might be of interest, sort of the basics for people to know?

Hochster People should get screening colonoscopies, and we have talked about that many times on this program because it can really prevent colon cancer. There are a number of very huge studies today that tell us conclusively that if you go regularly for a colonoscopy and you have adenomas removed, you will not get colon cancer.

Gore Those are the same as polyps?

Hochster The polyps, the adenomas. So, it is really important to go for screening colonoscopy because it can prevent you from having to deal with colon cancer. If someone is actually found to have colon cancer at the time of colonoscopy, because they finally get around to doing it or sometimes they have some rectal bleeding, they go to the doctor, the colonoscopy is done, and we find colon cancer, if it is in an early stage, usually we do surgery first and then depending on what the pathology looks like, if the lymph glands around the tumor are involved, then usually we will give additional chemotherapy for six months called adjuvant chemotherapy. So, if it is an early stage, stage I and possibly stage II, it is just surgery, and with stage II where the tumor is bigger, more invasive, but the lymph nodes are negative, then it is kind of a grey area about this adjuvant chemotherapy. If it travelled to the regional lymph nodes than we do give chemotherapy and if it has already spread beyond the colon and the lymph nodes, most typically to the liver when we talk about colon cancer, then usually we will start with chemotherapy, try to shrink things down and do surgery at a later day.

Chagpar Let's get back to this whole concept of personalized medicine and clinical trials and one thing that our listening audience might not know about Dr. Hochster is that he is also the Director of our Clinical Trials Office and personalized medicine is a big thing that we do here at Yale and I will tell you that one of the things that I have been particularly fascinated with is how well

people do on clinical trials, especially with these personalized therapies where we are finding genes or pathways that are mutated and we are targeting those pathways and people are doing incredibly well. Unfortunately, we have to take a quick medical minute now, but my question to you after that medical minute is going to be to talk to us a little bit about personalized medicine and how

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people on clinical trials may actually benefit from this breakthrough in molecular medicine, but first a medical minute, please stay tuned for information about colon cancer with our guest Dr. Howard Hochster.

Medical

Minute The American Cancer Society estimates that in 2014 over 45,000 new cases of pancreatic cancer will be diagnosed in the United States. Pancreatic cancer is the fourth most frequent cause of cancer death. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to make innovative new treatments available to patients. Clinical trial participation is offered for treatment of advanced stage and metastatic pancreatic cancer using chemotherapy and other novel therapies for the disease. FOLFIRINOX is a combination of five different chemotherapies is the latest advancement in the treatment of metastatic pancreatic cancer. There is continued research being done at centers like Yale and around world looking into targeted therapy and a recently discovered marker hENT1. 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 the WNPR, Connecticut's Public Media Source for news and ideas.

Gore Welcome back to Yale Cancer Center Answers. This is Dr. Steven Gore and I am joined tonight by my co-host Dr. Anees Chagpar and our guest Dr. Howard Hochster. We are discussing clinical trials in colon cancer and I am going to turn back to you Anees, because you were pretty excited to ask a question before our break.

Chagpar I really was. Thanks Steve. Howard, we were talking before the medical minute about personalized medicine and clinical trials and I was telling Howard that we have a clinical trial in breast cancer, which I think our listeners know is my area of expertise, for people who have mutation in their tumors for HER2, which is a commonly mutated gene in breast cancers, which is commonly tested for, and people on this clinical trial are getting two medicines, as opposed to our standard one medicine prior to surgery and are doing insanely well, like blow your mind, these are phenomenal response rates.

Hochster It is not usual that we hear a surgeon speak like that so I tend to think that they are actually doing remarkably well.

Gore Well, there are not many surgeons like Dr. Chagpar.

Chagpar Thank you so much, but it is incredible, it is absolutely phenomenal the response rates that I am seeing. I have not seen anything like this in my 13 years of practice. It is so exciting. So, my questions to you are as follows, we always test for HER2 in breast cancer, so patients know whether they are HER2 positive or not. Do you always test for mutations out in the community for

17:18 into mp3 file <http://yalecancercenter.org/podcasts/2014%200803%20YCC%20Answers%20-%20Dr%20Hochster.mp3> colon cancer? And can you talk a little bit about whether you are seeing or anticipating the kinds of responses that we have seen in breast cancer using targeted therapy because, I will tell you, it blows my mind.

Hochster It is very interesting, this whole area and it is very exciting for me to hear your enthusiasm for your observations that these women are doing really well who are receiving the treatment you talk about. The idea of personalized medicine is that we can study the tumor to better determine who might respond to what kind of treatment. In breast cancer you have a very long tradition of doing this with hormone receptors and that is already more than 50 years old and people know that people that expresses a certain kind of protein that binds estrogen will do very well with hormonal therapy and they might not need chemotherapy. So, breast cancer already has a very big tradition of doing a lot of molecular testing and the HER2 testing you are talking about, is kind of just another step on the road of a molecular profile. In colon cancer, we do not really have that so far, I mean we have been much more oriented towards chemotherapy because it works much better and we did not have the kind of situation where hormones or other kinds of molecular therapy work. What is very common today is people are testing in the community for this KRAS mutation, because it tells you not to give a certain kind of drug. We would like more tests to tell what we can do to help people more, but knowing not to give a drug that would not have benefit is also very useful. The latest thing that has happened with the KRAS story is that there are another six mutations in both KRAS and a related molecule called NRAS that adds another 15% of people who should not get the drug. It kind of narrows down the focus making it even more specific to the individual patient by looking at what we are calling extended

RAST testing. So, that is something that is not being done in every place and there is no FDA approved test for that yet, but it is being done in the academic centers like here at Yale, and our molecular profiling labs have been doing these tests for seven or eight years already. So, as the clinical knowledge advances and as we find that these kinds of tests have clinical implications and clinical utility, then they become done more widely, but being in a clinical trial today, I always tell my patients, you will get tomorrow's treatment today. So that is the great thing. If you do have a BRAF mutation, chemotherapy is known to be less effective and so you have another great option now by getting drugs that are tailored for people who have this very specific BRAF mutation. The clinical trial that we are doing with the company Novartis is a combination of three very exciting drugs that I think are going to be very helpful for this group of patients, it is just too soon to know because we have only done very preliminary testing.

Gore Does that mean if I have a newly diagnosed metastatic colon cancer, either because I present that way or because I had resected and it has come back and I have this BRAF mutation, I can go straight on to your clinical trial without doing standard chemotherapy first or do I have to have had the chemotherapy and have it shown that it did not work?

Hochster This trial allows prior chemotherapy and I think requires it, so you would normally get standard chemotherapy, but usually people get started on chemotherapy before they even know about these

21:15 into mp3 file <http://yalecancercenter.org/podcasts/2014%200803%20YCC%20Answers%20-%20Dr%20Hochster.mp3> molecular tests. The physicians usually request it a little later, but we aren't, I do not think, in the position today to say you should get this before chemotherapy.

Gore I see.

Hochster But maybe a year from now we might.

Gore And if I am a patient, as we have been discussing, and let's say I am not down in New Haven, should I be asking my doctor to make sure he sends off these mutation tests or should I expect them to be done automatically, or can they be done afterwards on archival tissue or anything like that?

Hochster The tests are all done in tumor tissue that is in the pathology lab already. They do not require additional biopsies and it is not exactly a standard of care today for every physician in every community to send these tests, so I think it's worth discussing with your physician about if molecular profiling tests were done and if so, what does it show? Are there any trials that you might qualify for based on that?

Gore And I guess if your physician does know about it, they can have you download this radio show.

Hochster Absolutely. There are a lot of places that are doing these kinds of testing today where they can profile 200 to 300 genes in the tumor and come up with the ones that are mutated, which could provide hints for treatment and today we are kind of going away from the era where we gave chemotherapy, which was kind of broadly effective to the extent that it was effective, but it would pretty much treat cancer cells no matter what, because it kind of pulverizes them. These are more like surgical strikes. So kind of a difference between carpet bombing and laser-guided smart bomb. The targeted therapies are like the smart bombs, they really go to the cancer cell that has the bad driver mutation and turns it off.

Gore Are they less toxic?

Hochster They are probably less toxic. The toxicity is a little different. They are usually pills or antibodies which usually have few chemotherapy like side effects.

Chagpar I want to pick up on that, because a lot of our listeners, I mean we talk a lot about chemotherapy here on Yale Cancer Center Answers, but a lot of people are wondering about natural alternatives. Is anybody looking at herbs? Is anybody looking at alternative therapies? What is going on in that area with colon cancer?

Hochster I am glad you brought that up. We actually have a really fascinating trial that just started that we are doing here with our colleagues in Pittsburgh, at the University of Pittsburgh Medical Center, to

24:01 into mp3 file <http://yalecancercenter.org/podcasts/2014%200803%20YCC%20Answers%20-%20Dr%20Hochster.mp3> look at a Chinese herbal preparation which contains

four ancient Chinese drugs that have been purified pharmaceutically and characterized pharmaceutically. It is a medication that is an herbal preparation. It is kind of if you are going for medical marijuana, but they actually purified it and package it and you know how many milligrams of the stuff you are getting, it is like that.

Chagpar Just to pick up on that Howard, in the middle, and I will let you continue, but that is why a lot of alternative therapies have never been tested.

Hochster Right.

Chagpar It is because nobody really went through the rigor of making sure people knew what exactly was in it, so that they could do a clinical trial, right?

Hochster Right, so Dr. Yung-Chi Chen here at Yale Cancer Center in the Department of Pharmacology has spent the last 15 to 20 years developing this herbal preparation of these four Chinese herbs and turning them into a drug and it is now being produced by a drug company and the drug is anti-inflammatory and cuts down on the toxicity of chemotherapy in our early trials. So now we are doing a randomized trial that will definitively show whether these Chinese herbs can cut down on a certain kind of toxicity we are seeing in colon cancer therapy. Basically for people who have gotten one first line kind of chemotherapy and are going on to their second chemotherapy, we believe that this Chinese herbal preparation, which is called PHY906 for people who may have heard about this before, if it will cut down on some of the chemotherapy associated toxicity, so that is really coming from ancient Eastern Medicine, coming through some of the alternate medicine organizations, but it really has got a lot of science behind it and it is really very interesting science.

Gore That is really cool and I just have to betray my ignorance, which is that offline before the show you guys were talking about this trial, Dr. Chagpar used the Canadian pronunciation, which is herbs, and I am thinking, jeez I have never heard of that tumor gene and I am wracking my brain what is the "herbs" gene.

Chagpar Back to this trial, patients still get chemotherapy and this is really complementary, not alternative. It is not a substitute.

Hochster Yes, I am sorry. It is complementary medicine. It is actually funded by the Complementary Medicine Branch at the National Cancer Institute and is being done by your tax payer dollars at work through a grant from the National Cancer Institute and so half the people will get the active drugs, half will get placebo, and then we will really be able to compare the side effects of the chemotherapy, but everyone is getting the active chemo.

Chagpar And it would seem to me that if this preparation reduces inflammation, reduces side effects, that could be something that could cross cut across different types of cancer and different types of therapy, right?

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Hochster Absolutely, we are looking at it with other kinds of drugs including some targeted ones to cut down some of the skin toxicity as well.

Gore Do they use these particular herbs in China with chemotherapy already?

Hochster I think that it is mostly used as an alternative, but here it has really been used in the complementary fashion as Dr. Chagpar points out.

Chagpar So for right now this trial is only for people with colon cancer, or are you opening it up?

Hochster This is specifically for colon cancer, people getting what we called second line chemotherapy.

Chagpar So, if lots of people go into that trial, and we find out that it is actually beneficial, then is it something that we could try in breast cancer?

Hochster Absolutely.

Chagpar I'm looking at this going, I want to get my hands on this preparation. What else do you see coming down the pike in terms of colon cancer that is new and interesting?

Hochster Well there are other kinds of targeted agents where we are looking at very specific markers and then finding the right treatment and I have been spending many hours over the last six months with my colleagues from around the country and at the National Cancer Institute to come up with a molecular profiling trial in colon cancer. This will be a national trial sponsored by the National Cancer Institute, where we will get people's tumors and then we will actually run a couple hundred gene molecular profiles and find out what the best treatment is for that patient and then they will be assigned to a trial that will be appropriate to their particular kind of characteristic tumor. So, again, this is what we call kind of a molecular treatment profiling trial. We also have some what we call bucket trials where if you have this kind of mutation like BRAF for example, but you have a different kind of cancer, a gallbladder cancer, stomach cancer, or even a breast cancer, we have a trial now that is going on where anybody who has got the BRAF mutation can get the drug irrespective of the diagnosis, so we are moving a little bit away from specific diagnoses and are trying to treat people based on their molecular diagnosis.

Dr. Howard Hochster is Professor of Medicine and Medical Oncology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voice mail 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 addition of Yale Cancer Center Answers here on WNPR Connecticut's Public Media Source for news and ideas.