



Immunotherapy and the Treatment of Triple Negative Breast Cancer

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Welcome to Yale Cancer Answers with doctors Howard Hochster, Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and specialists, who are on the forefront of the battle to fight cancer. This week in honor of breast cancer awareness month, it is a conversation about immunotherapy and the treatment of triple negative breast cancer with Dr. Lajos Pusztai. Dr. Pusztai is a Professor of Medicine and Medical Oncology at the Yale School of Medicine and Dr. Chagpar is an associate Professor in Department of Surgery at the Yale School of Medicine and the assistant director for global oncology at Yale Comprehensive Cancer Center.

Chagpar So, Lajos, you know as breast cancer awareness month goes on, a lot of women are going to be hearing about breast cancer, but we understand that breast cancer is more than one disease, that there are different kinds of breast cancers and one of the kind that worries a lot of women is triple negative breast cancer. Can you tell us a little bit more about what exactly that is?

Pusztai You're absolutely right. So one of the most important break throughs in the past 10-15 years in breast cancer research has been the realization that breast cancer is really at least 2 major disease types and they are different in the sense that their molecular makeup, the risk factors that predispose or protect women to develop them are different and they probably also originate from different subtypes. So the 2 major types are the estrogen receptor positive cancers and the estrogen receptor negative cancers, and you also have a third category that we refer to as HER-2 positive. HER-2 refers to a cell surface molecule which is a wonderful target for a highly effective treatment like trastuzumab and other similar drugs. Triple negative breast cancer refers to a subtype which is negative, which does not possess or have the estrogen receptor or progesterone receptor which are 2 female sex hormones or HER-2 protein on its surface. So triple negative breast cancer accounts for probably 15% of all annually diagnosed breast cancers.

Chagpar And so, why should we hear about triple negative breast cancer, what is special about it, aside from the fact that it does not have these receptors?

Pusztai Triple negative breast cancer is special in many ways. We have fewer therapeutic options for these patients and the options are primarily surgery, chemotherapy, and radiation, but there are some really exciting new discoveries in this field that probably will change this within the next 1 or 2 years and these are immunotherapies, particularly in the early stage setting. Triple negative breast cancer is also unique in the sense that it is a more rapidly growing tumor more frequently than the other types. It is diagnosed by women on self by patient feeling a lump growing their breast as opposed to just being picked up a routine screening mammogram.

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- Chagpar And so, triple negative cancers, they tend to be a little bit more aggressive and because they do not have these receptors, there fewer targeted agents and that is why chemotherapy is really what is used. Before we jump into the exciting parts of immunotherapy, can we talk a little bit of the epidemiology of triple negative breast cancer because there is a lot of stuff on the internet and people read about triple negative breast cancer and they hear about it being really aggressive, but it only affects 15-20% of patients. Does it affect younger women, more African-Americans, is there a genetic predisposition, who exactly gets triple negative breast cancer?
- Pusztai Yes, this is a very important question and you're absolutely right. So there is a little bit of misconception about triple negative breast cancer in the public space. So first of all, I would like to reiterate that the vast majority of breast cancer patients who are diagnosed with the triple negative breast cancer at early stage, there is cancer in the breast or in the lymph nodes or in the armpit are cured. So they will be cured with currently available therapies. This cure rate is a little less than for the estrogen receptor positive cancers, but it is still in the 70% range. With regards to the risk factors for triple negative breast cancer, these are different from the risk factors that usually associate with breast cancer in general because those tend to be the risk factors that predispose women for the other type, the more common type of breast cancers which is the ER positive or estrogen receptor positive cancer that of course accounts for the vast majority of 70% or so of breast cancers. So unlike for estrogen receptor positive breast cancer, the lack of pregnancies actually is somewhat of a protective factor and lack of breastfeeding is a risk factor to develop triple negative breast cancer. They also tend to occur in younger women and also it is a little bit more prevalent among African-American patients compared to other races.
- Chagpar And what about genetic predispositions, are more people who get triple negative breast cancer, is that associated with BRCA gene mutations and so on, or is that independent?
- Pusztai So genetic predisposition which refers to a condition when someone inherits a gene from the parents that predispose a person to develop a particular cancer like breast cancer, it really underlies probably less than 10% of all breast cancers and there are 2 sort of important genes which account for most of these hereditary forms of breast cancer and these are the BRCA or BRCA-1 and BRCA-2 genes. With BRCA-1 genes, if someone inherits a somewhat faulty BRCA gene, the likelihood to develop triple negative breast cancer is much higher than to develop any other type of breast cancer, but again this still is a minority of triple negative breast cancers that arise in these genetic backgrounds.
- Chagpar And so clearly the risk factors are a little bit different, but this is still minority of patients, but let us suppose somebody is diagnosed with triple negative breast cancer and you know, are their surgical options the same as if they had any other kind of cancer or they necessarily treated more aggressively surgically?

- Pusztai I am somewhat embarrassed to answer this because you are the surgeon of the breasts, but of course, as you know the surgical options are very similar except for patients who actually do develop these type of cancers in the context of a BRCA germline mutation, in other words they inherited this faulty gene. These individuals unfortunately are high risk to develop a new breast cancer either in the same breast or in the other breast and they are also at risk to develop ovarian cancer. So for this relatively small subset of patients, we do recommend bilateral mastectomies, but for all other patients a lumpectomy followed by radiation therapy is a perfectly safe and appropriate treatment option.
- Chagpar Yeah, so from a surgical standpoint whether you are triple negative or whether you are estrogen receptor positive which is as Dr. Pusztai mentioned, the vast majority of patients that we see, surgical options are pretty much equivalent and so discussing with your surgeon which is the best option in your particular case is the best thing to do and really the receptor status will have little impact on the surgery. Where it has more impact is really in your field Dr. Pusztai of the medical oncology treatments because the targeted treatments for the estrogen receptors, the targeted treatments for the HER-2 receptor are no longer available to you and so many patients ask the question of does that mean that this cannot be treated then and I think your answer was, no you can still be treated, but the treatment options are different.
- Pusztai That is correct and also, it is very important to keep in mind that really in all kinds of cancers including breast cancer as well there are 2 really very fundamentally different stages of the disease. We think of breast cancers either as early stage disease or late stage disease. Early stage disease often times described medical terminology as stage I, stage II, or stage III breast cancer and late stage disease is stage IV or metastatic cancer. Fortunately, 95% or more of breast cancer patients are diagnosed initially, within early stage disease that is clinically stage I, stage II, or stage III. At these stages, the cancers are highly curable, it is really important that someone receives a proper yet an aggressive therapy because that is a chance to really save someone's life and really avoid distant metastatic recurrence of the tumor. Metastatic disease or stage IV disease can be newly diagnosed or could develop as a recurrence, as a relapse, or a reoccurrence of the cancer in another site, in a distant site, in another organ other than the breast, like local lymph nodes. So that late stage disease unfortunately is still incurable, but fortunately the vast majority of patients present with an early stage disease where the cure rates are very high 80-85%.
- Chagpar And so how do you treat somebody who has a triple negative cancer who is early stage?

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- Pusztai So the extensive care or state of the art treatment usually involves 3 components, surgery, chemotherapy, and radiation therapy. The sequence of these can vary and increasingly, the most intelligent sequence is probably to start with chemotherapy first. The goal of chemotherapy is really to eradicate or kill runaway cells that may have left the breast or the surrounding lymph nodes and hide somewhere in the body, in liver, lung, bone, or any other organs. So chemotherapy can reach these runaway cells and eradicate or kill them, that is the main purpose of the chemotherapy. By doing the chemotherapy first before the surgery, obviously one could directly measure the impact or the efficacy of the treatment, because if there is no cancer left or no cancer survived the treatment by the time a patient reaches surgery, that is a very good news. So obviously the chemotherapy worked very well. If there is residual cancer that survived the initial treatment, it also offers an opportunity to receive additional treatment after the surgery that has been shown to improve survival.
- Chagpar And so, tell us more about the chemotherapy options that women with triple negative breast cancer have, the side effects that they can anticipate, I mean people who have triple negative breast cancer when they first hear the word chemotherapy as really their option in terms of medical management of their cancer, often are faced with trepidation, they worry about their hair falling out and what that will mean for their lives in terms of symptoms and side effects. Can you talk a little bit more about that?
- Pusztai Of course, these are very valid and appropriate concerns and unfortunately, many patients do experience side effects on the chemotherapy, but the important points to really keep in mind is the chemotherapy improves survival, it improves the chance that someone would actually avoid a much more difficult and much more complicated and toxic therapy in the future where the hope of cure no longer exist. Unfortunately, side effects of chemotherapy include many different types of symptoms. The most common is hair loss, fatigue, muscle aches, joint pains, flu-like symptoms, neuropathy - somewhat depending on what type of chemotherapy regimen one uses. Most of the side effects, however, improve or even completely resolve after the treatment is completed.
- Chagpar How long is treatment, I mean do people have to get chemotherapy every day for weeks or months or years on end, or is this kind of a more isolated course?
- Pusztai There multiple different types of chemotherapy regimens which are all more or less equally effective or good, and the duration of treatment ranges from between 16 to 20 weeks.
- Chagpar And it is not every day right?
- Pusztai It is not every day. So treatments, either of the most frequent treatment is the weekly treatment that would last for 12 weeks followed by 4 additional treatments with a different kind of chemotherapy that is given every 2 weeks. Other regimens include treatments once every 2 weeks for 8 treatments. They have subtle pros and cons and it is important to discuss with the medical oncologist.

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Chagpar So we are going to learn a lot more about all of those medical treatments as well as a new innovative treatment like immunotherapy right after we take a short break for a medical minute. Please stay tuned to learn more about triple negative breast cancer with my guest, Dr. Lajos Pusztai.

Medical Minute

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There are many obstacles to face when quitting smoking as smoking involves the potent drug, nicotine, but it is a very important lifestyle change, especially for patients undergoing cancer treatment. Quitting smoking has been shown to positively impact response to treatments, decrease the likelihood that patients will develop second malignancies, and increased rates of survival. Tobacco treatment programs are currently being offered at Federally Designated Comprehensive Cancer Centers, such as Yale Cancer Center and at Smilow Cancer Hospital. Smilow Cancer Hospital's tobacco treatment program operates on the principles of the US Public Health Service Clinical Practice Guidelines. All treatment components are evidence based and therefore, all patients are treated with FDA approved first line medications for smoking cessation as well as smoking cessation counseling that stresses appropriate coping skills. More information is available at YaleCancerCenter.org. You are listening to WNPR, Connecticut's public media source for news and ideas.

Chagpar Welcome back. This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Lajos Pusztai. We are talking about triple negative breast cancer and Lajos right before the break, we were talking about chemotherapies and different kinds of regimens and the side effects, but there is a lot of innovative things going on in this space with really smart people trying to figure out how we can treat triple negative breast cancer better and one of the things that you mentioned rather in passing in the last segment was immunotherapy for early stage disease. Can you tell us a little bit more about what exactly is immunotherapy and what results can we expect with that in triple negative breast cancer?

Pusztai So immunotherapy is the first treatment strategy where we would somehow excite and increase the activity of a person's immune system to fight cancer. This has been really an elusive holy grail of cancer research for many decades until about 7 or 8 years ago when highly effective new therapies started to appear in the clinical trial scene and the first drugs that approved a few years ago in the metastatic lung cancer, melanoma and they have shown remarkable efficacy in this otherwise, very difficult to treat cancer types and most importantly, patients who benefited or responded to these treatments tended to have very durable responses. So all these drugs, these immunotherapy drugs and the most advanced among them are called immune checkpoint inhibitors are also being tested in metastatic breast cancer, in early stage breast cancer, and the greatest activity actually appears to be in triple negative disease.

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- Chagpar And so have there been studies looking at triple negative breast cancer and immunotherapy, I mean is this is something that is standard of care or there are clinical trials looking at this?
- Pusztai So these drugs are not yet standard of care for breast cancer. They are standard of care in many other cancer types. In breast cancer, we have several clinical trials, both in the metastatic or advanced stage disease and also in early stage disease, and I am very proud to tell you that the first sort of early stage disease studies with these agents actually opened at Yale in 2015 and we took an immune checkpoint inhibitor drug and combined it with the standard of care neoadjuvant or preoperative chemotherapy regimen, and we found that the efficacy of the chemotherapy has increased dramatically when the immune checkpoint inhibitor or the immunotherapy was added to the treatment and these did not come with any significant added toxicity or more side effects. To put this into context, I refer to this in the earlier segments of this discussion that when chemotherapy is given before surgery, some patients experience complete eradication of the cancer. We call this pathological complete response. This occurs about 30-35% of the time with chemotherapy, even with the best chemotherapies. In this clinical trial where we added a immune checkpoint inhibitor to the chemotherapy regimen, what we observed was a 70% pathological complete response rate, that is more than doubling of the efficacy of the treatment, so we are very excited about this. The study is still ongoing and there are several other studies which are opening in various parts of the country and there are at least two large registration trials also ongoing where the purpose of the studies do definitively show that this is better than chemotherapy alone leading to an FDA registration so that these become standard of care.
- Chagpar And the important thing to really point out is that pathological complete response rate has been thought of as a surrogate for outcome. So when you can double the pathologic complete response rate of really in genders hope that these patients are going to do very well with the immune checkpoint inhibitor.
- Pusztai Yes, that is a very important clarification. So the importance of this complete eradication of the cancer from the breast and lymph nodes before surgery is that these patients have an outstanding longterm survival, cancer-free survival.
- Chagpar And so, Lajos, you said that there really was not an increase in toxicity. Is there a difference in the toxicity that patients have with immunotherapy versus chemotherapy? Are there are other side effects that they should anticipate?

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- Pusztai Yes, the side effects from immunotherapies are very different from the side effects of chemotherapies. Chemotherapies tend to hurt tissues and cells that grow or proliferate rapidly like someone's hair or the lining of the mouth or gut. Immunotherapy on the other hand works by boosting the immune system and sometimes we over boost the immune system leading to autoimmune reactions or autoimmune syndromes. So it is a very broad range of autoimmune diseases that one could actually observe as a side effect during immunotherapy, but thanks for god, these are rare, and rare means that the effect in patients in single digit person numbers like 1, 2, 3, 4%.
- Chagpar Ok and so there are some really exciting therapies on the horizon with immunotherapies in early stage triple negative breast cancer. What are we doing in metastatic breast cancer, what are the advances there?
- Pusztai So in metastatic triple negative breast cancer, immunotherapies also show promise. The response rate, there is tumor shrinkage occurs, unfortunately still in the minority of patients, probably between 5-20% the most. However, just like the other cancer types those who respond tend to experience and enjoy a really prolonged sort of progression or cancer growth-free survival and that is really a very important observation, and in many ways very different from what we use to see with chemotherapy where response rates may be higher but the duration of the response is much shorter. So the real challenge in the metastatic setting is to find the best partners to really improve the efficacy of the immunotherapy drugs and there are exciting studies which combine different types of immunotherapies together.
- Chagpar So can you tell us more about that - what clinical trials might be available for patients?
- Pusztai So we have clinical trials that combine just like in the early stage setting, combined chemotherapy with immunotherapy. We also have clinical trials that combine existing checkpoint inhibitors which are the most advanced form of immunotherapy today with other more investigational and more novel approaches to immunotherapy. These tend to be treatments which in some way or in some shape or form increase the activity of the immune system, but in addition to the immunotherapy approaches there are several other really promising new therapeutic approaches that are appearing in the metastatic scene for triple negative breast cancer.
- Chagpar Like what?

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- Pusztai For example, antibody drug conjugates. Antibody drug conjugates refer to a new type of treatment where one generates an antibody that hones in and finds a particular antigen or a particular marker of a cancer cell and to the antibody, there is a chemotherapy drug attached. So advantage of this combination of attaching the chemotherapy to the antibody is that the chemotherapy does not circulate or does not float around freely in the blood and does not cause the same amount of side effects as it would otherwise. The antibody serves as an address to really to target the chemotherapy drug to the right cells which are the cancer cells in this particular instance. There are 2 or 3 drugs in this category we'll just refer to them as antibody drug conjugates or ADCs which have shown remarkable efficacy in metastatic triple negative breast cancer and they probably- at least one or two of them - will appear in the market hopefully within the next one year or so, but in the mean time they are available for patients in the context of clinical trials.
- Chagpar So it sounds like this is really developing a targeted therapy for something that was previously not targeted.
- Pusztai That's right, it is possible to think about this as targeted chemotherapy where the chemotherapy drug is targeted to the cancer cells with the help of an antibody.
- Chagpar And finally, you know we had talked in the earlier segment about BRCA associated cancers and the fact that some triple negative cancers occur in people who have a defective BRCA gene or a mutation. Is there progress being made to look at that subset of patients and see whether there are drugs that will be particularly efficacious in that population?
- Pusztai Yes, BRCA gene itself helps to repair damaged DNA and cancer cells very often have DNA damage as part of the rapid proliferation and growth, and when they have a BRCA mutation, they have difficulty repairing the DNA and DNA damage which is a certain level, then cells no longer can tolerate and they die. However, most of the time, the damage that the BRCA mutation causes is still tolerated by the cancer cells. So chemists and scientists developed a molecule which actually can block the activity of other DNA repair mechanisms and therefore, pushing the cell beyond this tolerable amount of DNA damage. The most advanced among these new class of drugs, we call them PARP inhibitors is olaparib. And olaparib has been approved to treat BRCA positive or BRCA mutant variant cancer, and a similar study in metastatic triple negative breast cancer in fact have shown that patients who are BRCA positive and receive this treatment also do much better than patients who are BRCA normal or who have standard of care treatment as a comparative arm. So again, we are very hopeful in the medical community that these drugs will soon be available for BRCA positive triple negative breast cancer patients, who have metastatic cancer.
- Chagpar Is there similar effort being made in early stage for patients who have BRCA associated triple negative breast cancer and using PARP inhibitors in that population?

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- Pusztai Yes, so when drugs usually start at development phase in metastatic disease trying to prolong the survival of patients or hoping for maybe even curing some patients with the advanced metastatic disease. Once they show efficacy, then they usually are taken to this early stage disease setting with the hope that we would actually improve cure rates in the early stage disease. So it is a large clinical trial that is still ongoing where a PARP inhibitor like olaparib is used after surgery. Patients will take the pill for a year and compare to a placebo pill. We hope that the patients who are receiving the olaparib drug will have in improved survival and improved cure rate. Again, this is a clinical trial that is available at Yale and several other large academic centers throughout the country and in fact, throughout the world to test the efficacy of the PARP inhibitor as adjuvant therapy for early stage BRCA positive breast cancer. This adjuvant trials also include patients who are estrogen receptor positive, so this is open for both Triple negative and estrogen receptor positive early stage cancer that arose in the background of this genetic susceptibility.
- Chagpar And Lajos, did you just say that it is a pill, so it is not IV chemotherapy, do people still lose their hair and stuff, or is it a pill like a tamoxifen pill?
- Pusztai That's right, it is a like a tamoxifen pill, it is like a blood pressure pill. It is a pill that patients take once a day for 1 year and the side effects are different from the side effects with chemotherapy. It does not cause hair loss and many of the other side effects that the patients may experience with chemotherapy like nerve damage, nausea, vomiting, mouth sores, diarrhea. These are rare with olaparib.
- Chagpar So there is a lot of exciting developments and you know, we must have mentioned clinical trials about 50 times in the last segment and I just thought you know, could you tell us a little bit more about clinical trials because, I mean certainly it is the way to get novel exciting therapies into the clinic, but a lot of patients are really anxious about enrolling in a clinical trial. How do you allay their anxieties when they say to you, I do not want to be a human guinea pig?
- Pusztai These are valid concerns because of course clinical trials, test drugs, that we do not know how well they work, but drugs that make it to the clinical trial stage usually have some very strong and very powerful rationale to suspect that they would work at least to some extent because they have worked in multiple different animal models, their safety has been tested in all kinds of animals and all kinds of experimental systems and they usually also by the time they arrive for large efficacy studies, they also have been tested in patients. Probably the better way to think about clinical trials is an opportunity to receive tomorrow's drugs today. It is really important to remember that every single drug or treatment that patients receive today and improves their outcome used to be an experimental drug a few years ago or used to be some form of an experimental treatment. So by participating in clinical trials, a patient really provides an opportunity for herself to receive treatment that might become the standard of care in the future.

Dr. Lajos Pusztai is a Professor of Medicine and Medical Oncology at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against the cancer. You are on WNPR, Connecticut's public media source for news and ideas.