Program Title: Endocrine Therapies for Breast Cancer

This program is being presented in partnership with White Plains Hospital

Originally recorded on: June 5, 2023

Moderator: Robin Perlmutter, LMSW- Support Connection Peer Counselor

Guest Speakers:
Dr. Karen Green, Medical Oncologist at White Plains Hospital in White Plains, NY graduated from New York University School of Medicine, where she was elected to the Alpha Omega Alpha Honor Medical Society and received the NYU Alumnae Club Award for the outstanding woman medical student. She was a resident in internal medicine and fellow in hematology/oncology at New York Hospital-Cornell Medical Center. After serving on the full-time faculty at the Weill Cornell Medical College for eight years where she specialized in breast cancer, she joined White Plains Hospital in 2003. She continues to focus her practice on breast cancer, and she also treats patients with a wide range of other types of cancer and benign blood disorders. At White Plains Hospital, she is the site principal investigator for the ECOG-ACRIN Cancer Research Group, and she is also the principal investigator or a co-investigator on a number of clinical trials. She serves on the White Plains Hospital Institutional Review Board and is a member of the White Plains Hospital Breast Program Leadership. She is an active member of the American Society of Clinical Oncology and the New York Metropolitan Breast Cancer Group.

Program Description:
Endocrine therapies are commonly used to treat breast cancer that is estrogen-receptor positive. Endocrine therapies may be used at different points in a treatment plan and to treat various stages of breast cancer. Dr. Karen Green, Medical Oncologist at White Plains Hospital in White Plains, NY, will present on the following topics pertaining to Endocrine Therapies for Breast Cancer:

- Endocrine therapy options
- Different contexts for use
- The latest updates
- Supportive care and management of side-effects

NOTE: You may find it helpful to view and listen to the slides from this webinar (which are posted on our website and YouTube channel) while reading through this transcript.

Robin Perlmutter: Good evening, everyone. I'm Robin Perlmutter, peer counselor here at Support Connection. I would like to welcome you all to our nationwide webinar on endocrine therapies for breast cancer in partnership with White Plains Hospital with speaker, Dr. Karen Green. Remember that Dr. Green is sharing her expertise, and any information from tonight or questions pertaining to individual concerns should be discussed with your doctor.

It's my great pleasure that we have Dr. Green, medical oncologist at White Plains Hospital. Dr. Green graduated from New York University School of Medicine, was a resident internal medicine and fellow in hematology and oncology at New York Hospital Cornell Medical Center. After serving on the full-time faculty at Weill Cornell Medical College for eight years, specializing in breast cancer, Dr. Green joined White Plains Hospital in 2003.

Dr. Green's focus continues to be practice -- her practice continues to have the focus on breast cancer while she also treats patients with a wide range of other types of cancers and benign blood disorders. Dr. Green is also a principal investigator on a number of clinical trials and serves on the

White Plains Hospital Institutional Review Board and is a member of the White Plains Hospital breast program leadership. Thank you, Dr. Green, for sharing your time and expertise with us tonight.

Dr. Karen B. Green: Thanks, Robin. All right. So I'm going to give an update on endocrine therapy for breast cancer. So, endocrine therapy is targeted therapy to treat breast cancer that is positive for the estrogen receptor and/or the progesterone receptor. Basically, it's the breast cancers that are estrogen receptor and/or progesterone receptor-positive are stimulated by estrogen. The binding of estrogen to the estrogen receptor stimulates these cells to grow and divide.

So this endocrine therapy is essentially anti-estrogen therapy that can be used in different settings of disease. It can be used first in patients who haven't even had breast cancer yet, but are known to have an increased risk of breast cancer. For instance, women who have the BRCA1 or BRCA2 gene mutation, or women who've had a biopsy that shows a diagnosis such as LCIS or atypical ductal hyperplasia or atypical lobular hyperplasia, which are associated with an increased risk for a subsequent development of breast cancer. When endocrine therapy is given in that setting, it's called chemoprevention. It's a chemical used to prevent a disease. Chemoprevention doesn't necessarily mean chemotherapy.

Endocrine therapy can also be used as neoadjuvant therapy. Neoadjuvant therapy means therapy that is given prior to surgery. Prior to surgery for early stage breast cancer. So settings where we might give treatment prior to surgery. For instance, when the COVID pandemic first started and our ORs had shut down temporarily, for patients whose breast cancer was estrogen or progesterone receptor-positive, we were starting them on endocrine therapy prior to surgery to prevent progression while we were waiting for surgery. Also, neoadjuvant therapy, either endocrine therapy or in some cases chemotherapy, can be given prior to surgery to downsize a tumor or downsize the extent of axillary involvement, which can make surgery technically more easy and also can increase the chance of getting negative margins.

Endocrine therapy is commonly given as adjuvant therapy, which means treatment after surgery in the case of early stage breast cancer to help prevent occurrence. And also, endocrine therapy is used as treatment of metastatic hormone receptor-positive disease.

So when I talk about hormone receptor-positive, I mean either estrogen receptor or progesterone receptor-positive or the combination of the two. So it could be one or the other or the combination. Endocrine therapy can be used in premenopausal women and in postmenopausal women, though the agents we use differ a bit, as I'll explain as we get on in the talk.

So I want to go one more slide. I want to show you a schematic for estrogen receptor signaling. The estrogen receptor can either sit on the surface of the cell or be inside in the media inside the cell, which is called the cytoplasm. And estrogen that's in the bloodstream diffuses through the cell membrane, or binds the estrogen receptor on the cell, so here it diffuses through.

There's two different pathways. In this pathway right here, which is the called the nuclear pathway, estrogen binds the estrogen receptor. This complex goes inside the nucleus of the cell, which is the brain of the cell where the DNA lives, and it stimulates certain target genes that stimulate the cell to grow and divide or basically proliferat

And in this other pathway, using the estrogen receptor on the surface of the cells, estrogen binds the estrogen receptor on the surface of the cells, and that signals or triggers a whole cascade of different pathways that also cause the cell to grow and divide or proliferate.

So where does this estrogen in the bloodstream come from? In premenopausal women, it comes from the ovaries. Once a woman goes through menopause, her ovaries shut down, but estrogen is still made in other parts of the body. In postmenopausal women, the adrenal glands, which are small glands on the surface of the kidneys, produce male hormones. And those male hormones are converted to estrogen in tissues such as the fatty tissue or other tissues in the body through an enzyme called aromatase, which we'll talk about a little bit further. So this estrogen receptor -- estrogen binding the estrogen receptor, again, stimulates estrogen receptor-positive cells to proliferate.

So how do we know if a particular tumor is positive for estrogen or progesterone receptor or other receptors, for that matter? I want to show you this picture. This is a picture of the stains that the pathologist does in the pathology lab once we have a tumor specimen from a biopsy or a surgical resection. The top is four different tumors, looking with the classic stain called H&E, or hematoxylin and eosin. That's the classic stain that just shows us the architecture of the tumor, helps us decide if it's ductal or lobular.

And then we go on to do some immunohistochemical stains, looking for the estrogen receptor, the progesterone receptor and the HER2, or human epidermal growth factor receptor. So what we do with these immunohistochemical stains, they involve an antibody. The antibody binds a particular protein. So in the case of the ER stain, it's an anti-estrogen receptor stain that pigments brown where it takes up. So the brown indicates the presences of the particular protein you're looking for. So these two tumors, for example, are estrogen receptor-positive. These two are estrogen receptor-negative. These two are progesterone receptor-positive. These two are progesterone receptor-negative.

So this tumor is ER/PR-positive, HER2-negative, which is about 70% of breast cancer falls into that type. This tumor is positive for ER, PR and HER2. That's what we call triple positive. This tumor is negative for ER and PR and positive for HER2. And this tumor is negative for ER, PR and HER2. That's what we call triple negative breast cancer. But we're going to be focusing tonight on hormone receptor-positive breast cancer.

So I want to first talk about some agents that are considered endocrine therapy agents. The first agent I'm going to talk about is tamoxifen, which has been around the longest. Tamoxifen has been around since the 1970s. This is an illustration of how the different drugs work, so I'll show this slide two other times. The routine in the non-drug state is that here's estrogen, binds the estrogen receptor, goes into the nucleus and stimulates target cell genes. In the case of tamoxifen, tamoxifen also binds the estrogen receptor, and it acts as a competitor for the regular estrogen to bind the receptor. And when tamoxifen binds the estrogen receptor, that complex does not stimulate the genes inside breast cancer cells, unlike the estrogen/estrogen receptor complex. So this is a block. It's an antagonist in breast cancer cells.

But -- and if we can go back to the slide. Okay, right here. So these drugs are funny drugs, the drugs that fall into this category of selective estrogen receptor modulators. They bind the estrogen receptor, and it competes for estrogen. The interesting thing is they can have an antagonist effect, meaning anti-estrogen effect, on certain tissue types, but -- such as breast tissue, they act as anti-estrogens. But actually, on some tissue types, they actually have an agonist or pro-estrogen effect such as the uterus. Tamoxifen has a positive effect on the uterus, an estrogenic effect. It stimulates uterine tissue to grow and divide. And we'll talk about that later when we discuss the side effects.

There are two other agents. So the fact that they have antagonist and agonist effects, depending on the specific tissue type, is the reason why they're called selective estrogen receptor modulators, because their effect on the estrogen receptor depends on the select tissue type that we're talking about. So there are three drugs in this category. Tamoxifen, as I mentioned, which can be used in both premenopausal and postmenopausal women. And there are two other drugs: toremifene, also called Fareston; and raloxifene, also called Evista. You might be familiar with raloxifene also as an osteoporosis drug. That's where it was originally developed, but then it was -- it got approved also as a breast cancer prevention agent. These drugs, these last two, toremifene and raloxifene, have only been studied in postmenopausal women. So the FDA approval is only for postmenopausal women. So tamoxifen is the only one of these that's approved for premenopausal women. Next slide.

So what are side effects of SERMs? Side effects include hot flashes, vaginal discharge. In premenopausal women, there can be menstrual irregularities and frank menopause. They can also cause muscle cramps, and occasionally some patients get joint aches. Maybe there's an increased risk of cataracts, although it's not entirely clear that that's increased above placebo. There does appear to be an increase in fatty liver disease. So I do have patients whose liver enzymes go up on tamoxifen, and sometimes we actually have to stop the drug because of that.

There also is an increased risk of blood clot. The blood clots with tamoxifen are primarily venous, or you might have heard of the term DVT, deep vein thrombosis, as opposed to arterial blood clots. Arterial blood clots are the primary type of blood clots that cause stroke. But these are primarily venous, DVTs, and occasionally DVTs can embolize or spread to the lungs. That's called a pulmonary embolism. I will say, while the rate of blood clot is increased above compared with placebo, it's still overall quite low with tamoxifen.

There's also, as I had mentioned, tamoxifen has an agonist effect or pro-estrogen effect on the uterus, and that is associated with an increased risk of uterine cancer with tamoxifen. Again, this risk is increased when you compare it with placebo, but overall, the rate of uterine cancer is still quite low. So the benefits for the drug far outweigh the risks for the majority of women. And I will also comment that the risk of uterine cancer seems to be limited only to women who start the drug at age 50 or older. So our younger women in the 40s don't really have to worry about that risk.

The one cautionary tale with tamoxifen, in particular of the SERMs, is that there can be drug interactions. Tamoxifen when ingested is ingested in the inactive form, and it requires the CYP2D6 enzyme in the liver to be activated. And some drugs and some supplements are CYP2D6 inhibitors. So those block activation of tamoxifen, and there's some concern that they can interfere with the activity of tamoxifen. Some CYP2D6 enzymes inhibitors that become of concern, for instance, the drug Prozac is a strong CYP2D6 enzyme inhibitor. So when we start patients on antidepressants, we

have to be careful because some of them are similar to tamoxifen and do inhibit this enzyme. And I'll go through later a list of some that we consider safe and some that we try to avoid.

Some herbal supplements also inhibit the CYP2D6 enzyme. Something called St. John's Wort, which was a popular antidepressant in the 1990s, let's say, that has been shown to inhibit this enzyme and interfere with tamoxifen activity.

Next, I want to talk about a group of drugs called aromatase inhibitors. As I mentioned, aromatase is the enzyme that's responsible for production of estrogen in the fatty tissue and other tissues in postmenopausal women. So these drugs inhibit that enzyme, and that leads to suppression of estrogen production that takes place in postmenopausal women outside the ovaries. This class of drugs includes three, three drugs: anastrozole, commercially known as Arimidex; letrozole, commercially known as Femara; and exemestane, commercially known as Aromasin.

These drugs really only work when you give them alone in postmenopausal women because premenopausal women are still making so much estrogen in their ovaries. So if we're going to use them in a premenopausal woman, then we have to first give some ovarian function suppression to the premenopausal women before we could use an aromatase inhibitor.

And how do we suppress the ovaries in premenopausal women? Most commonly, we use one of a class of drugs called GnRH agonists. These include Lupron. That's the commercial name. The chemical name is leuprolide. Or another commercial name, Zoladex, or goserelin. These drugs are given as intramuscular injections monthly or every three months, and they work by working on the pituitary gland in the brain. Normally, the pituitary gland sends stimulatory signals to the ovaries, but these block the pituitary gland from sending those stimulatory signals to the ovaries. So the ovaries essentially shut down and that leads to a reversible menopause. The good news about these medications is if a premenopausal woman goes on one of these medications and finds that they cannot tolerate menopause, the symptoms of menopause, then we just can stop the drug and the effects can wear off.

We also have oophorectomy, which is surgical removal of the ovaries. However, that's permanent. That's irreversible menopause. So one might try a GnRH agonist first and make sure a woman can tolerate -- a premenopausal woman can tolerate and deal with the side effects of menopause before doing an oophorectomy as a way of suppressing her ovaries.

We also have ovarian irradiation. But I would say nowadays, that's rarely used due to radiation having some other side effects and us trying generally to avoid radiation.

So what are some side effects of ovarian function suppression and aromatase inhibitors? Well, they can cause hot flashes. There can be vaginal dryness and/or sexual dysfunction. There can be hair thinning. There can be a constellation of musculoskeletal symptoms, such as joint aches, joint stiffness, muscle aches and bone pain. There also is an increased risk of carpal tunnel syndrome. And some women say their thinking is a little bit slowed or their memory is a little bit dampened. So cognitive and memory issues with us decreasing the estrogen level.

So how do AIs compare with tamoxifen? AIs are those aromatase inhibitors, again. How do they compare with tamoxifen? Well, they have a higher risk of osteoporosis. I forgot to include here in this list, a side effect is a decline in bone density with aromatase inhibitors. So there's a higher rate of osteoporosis and bone fractures. There's an increased risk of cardiovascular disease, diabetes and high cholesterol levels. However, there's a lower risk of venous blood clot and uterine cancer with AIs.

Moreover, AIs are more efficacious than tamoxifen. A number of studies in the 1990s first showed in the metastatic setting and then showed in the adjuvant study that AIs have greater efficacy than tamoxifen. So due to the greater efficacy than tamoxifen and the lower risk of venous blood clot and uterine cancer, which in rare cases, rare cases, can be life threatening or fatal in very rare cases. But due to that, AIs have become generally the preferred agent for postmenopausal women.

In premenopausal women, ovarian function suppression plus AI has been shown more recently in long term follow-up to improve progression-free and even overall survival in women, particularly women with high risk features. So ovarian function suppression and AI has also become a preferred option for premenopausal women with high risk features.

I will also comment here that ovarian function suppression plus tamoxifen is also an option with perhaps a little less side effects for the premenopausal women and a little greater efficacy than tamoxifen alone. So that's also an option for premenopausal women. And again, it's really the high risk women. And we find those are women who with their breast cancer diagnosis less than age 35, or those who need adjuvant chemo -- have particularly high risk disease and they need adjuvant chemotherapy, those are the women who seem to benefit most from ovarian function suppression plus AI as opposed to tamoxifen.

So I'm going to now discuss some of the specific side effects of ovarian function suppression and AIs and how we manage those. So first, I'm going to talk about the musculoskeletal symptoms. The first line of management is exercise. Exercise lubricates the joints. Movement lubricates the joints. Exercise strengthens muscles so there's less stress on the joints. Exercise helps with weight reduction so there's less stress on the joints. And exercise helps the body release those feel good chemicals, endorphins, so that people's pain threshold is actually higher. Another agent that can be helpful are non-steroidal anti-inflammatory drugs such as ibuprofen, Advil, naproxen.

Another strategy that we commonly use is temporary discontinuation of the aromatase inhibitor that a patient is on. So holding the drug for anywhere from one up to like five weeks or so to allow the effect of the drug to dissipate and then a trial of a different AI. Often with a little break, what we call treatment holiday, and institution of a different AI, one of the other two agents, patients do find improvement in their symptoms often with that approach. And we do consider that temporary discontinuation of the AI safe.

A medication that has been shown to be helpful is duloxetine, or commercially known as Cymbalta. That is one of the SSRIs. Studies with that agent have shown it to help ease musculoskeletal symptoms on AI. Acupuncture has shown to be helpful. And in some cases, we do switch to tamoxifen, because overall, the musculoskeletal symptoms on tamoxifen are generally less.

What about management of vaginal dryness? So non-hormonal vaginal moisturizers and water-based lubricants, those are our first line agents used for mitigation of the symptoms. Water-based lubricants are short acting. Short acting. They're water-based. They are helpful with sexual intercourse and sexual interactions. And two common ones are Astroglide and Uberlube. Those are very popular agents.

The non-hormonal vaginal moisturizers, those are a little more long acting. And they help with maintaining the vaginal health, the health of the lining of the vaginal. And some that are commercially available in the retail stores like CVS and Rite Aid are Replens, Vagisil makes a vaginal moisturizer, and Luvena is another one commercially available.

There are two called Revaree and another one called HYALO GYN, which are hyaluronic acid suppositories. Hyaluronic acid is a very good moisturizer. So these are very, very helpful for a lot of patients. Little suppositories that they can be used like -- they can be used every day, but they're a little more expensive. So typically, we use them two to three times a week and supplement them with other moisturizers if needed.

Something else that we can use to supplement them is organic, unrefined coconut oil. I have a lot of patients who find that helpful. I do suggest if you do try that, that you first use it on your arm. Place it on your arm, your forearm, and leave it there for 24 hours just to make sure you don't have an allergic reaction to it before you use it intravaginally or on the vulva. I've heard of patients using olive oil. I've heard of patients using Crisco. Those are other options that people use. And again, these can be used in combination or alone.

Well, what about vaginal hormones? So there's vaginal estrogen. There's vaginal DHEA, which is also called Intrarosa or Prasterone and vaginal testosterone. The concern with these agents is that they do have some absorption, and they have been shown to increase the estrogen level in the blood a little bit. Whether this really increases the risk of breast cancer isn't entirely clear, and I don't think we're ever probably going to get an answer to this.

Most studies that have looked at this don't seem to show an increased risk of breast cancer with these medications. There was one study that did show an increased risk of -- I don't mean an increased risk of breast cancer. I mean an increased risk of recurrence, breast cancer recurrence. One study did show an increased risk of recurrence, but there were limitations with that study. So again, really unclear.

I do allow my patients to use these medications if they are still quite symptomatic, despite use of the first line moisturizers and lubricants. And I do say that if patients are going to use vaginal estrogen, I prefer Vagifem or Imvexxy. Those are two particular agents. I prefer those over an estrogen cream, such as Estrace cream or Premarin cream. The reason being these are intravaginal estrogen tablets. They're inserted intravaginally. They are less absorbable. They're absorbed at a lower rate than estrogen cream. And the amount of estrogen that is in them is lower dose. So I generally prefer these if I'm going to use vaginal estrogen in a patient.

The other thing is it does appear that these -- theoretically, these may be safer in women on tamoxifen since it is an estrogen receptor blocker, compared with women on aromatase inhibitors. That being said, women on aromatase inhibitors, they may do better with a DHEA or testosterone

because the aromatase inhibitor may block conversion of these agents to estrogen.

I'll also mention laser, which you might have heard of something called the MonaLisa. That's one laser brand. Laser has been shown to be helpful to alleviate some of the symptoms of genital -- what we call genitourinary syndrome of menopause. The vaginal dryness and other frequent symptoms such as urinary frequency, urinary tract infections is called genitourinary syndrome of menopause. Laser can be helpful for the vaginal symptoms. However, laser is not covered by insurance, and it is expensive. And if it's not used in skilled hands, it does have some risks, such as small, small risk of vaginal perforation.

What about management of hot flashes? So here, the SSRIs, which stands for selective serotonin reuptake inhibitors, and the SSNRIs, which is selective serotonin norepinephrine reuptake inhibitors, these are a class of drugs that generally were developed as antidepressants and antianxiety medications, but they have been shown to mitigate hot flashes.

The one concern, as I mentioned before, is some of these medicines are strong CYP2D6 inhibitors, so they interfere with the activation of tamoxifen in the body. So the two that are strong CYP2D6 inhibitors are Paxil, or paroxetine, and Prozac, which is also known as fluoxetine. But the ones that we do consider safe on tamoxifen because they are weak inhibitors of CYP2D6 are venlafaxine, commercially known as Effexor; desvenlafaxine, commercially known as Pristiq; citalopram, commercially known as Celexa; duloxetine, commercially known as Cymbalta; and escitalopram, hopefully I'm pronouncing that right, correctly, commercially known as Lexapro. So these can be very helpful.

The medication gabapentin can be helpful. Gabapentin was originally developed as an anti-seizure medicine -- seizure medication. Then it was shown to help with nerve pain, neuropathic pain. And more recently, it's been shown to help alleviate hot flashes. Gabapentin has a side effect of sleepiness, so we take advantage of that. Gabapentin I find particularly useful in patients who have night sweats and sleep disturbance from the aromatase inhibitors. So they take it at bedtime, and they can both have relief of their night sweats and sleep well through the night. Can be very helpful.

There's one other drug that I forgot to include on this slide, and that is oxybutynin, which is also known as Ditropan. That's a drug that was initially developed for overactive bladder symptom. That drug has anticholinergic side effects. That anticholinergic side effect inhibits sweating. So it was studied and found to be useful in alleviating hot flashes.

I'm going to skip that for now. I wanted to mention a group of drugs now called selective estrogen receptor downregulators, or SERDs, as opposed to before, we talked about selective estrogen receptor modulators, or SERMs. These SERDs, I show you on the schematic, they bind the estrogen receptor, and that leads to degradation of the estrogen receptor. So we don't have to -- they are complete estrogen antagonists. We don't have to worry about that agonist effect that we see with the SERMs in some tissues like the uterus.

So we have at this point in time two approved drugs in this class. The first -- for quite some time, we only had one drug, which is fulvestrant, commercially known as Faslodex. And that's available as an intramuscular injection given monthly. Except the first month, it's given twice in that month

because it requires a loading dose. And that's approved for metastatic estrogen receptor-positive breast cancer. It's not approved for early stage breast cancer. However, I will say that I have used it in a few patients with early stage breast cancer in whom I've been able to get insurance coverage for it. Since it's not FDA approved for early stage breast cancer, some insurances may not cover it in early stage breast cancer. But in one particular patient I'm thinking about, she couldn't tolerate -- we went through all the three aromatase inhibitors, and she had some contraindications to tamoxifen. So I was able to get approval for this agent. And I generally find this agent has less musculoskeletal side effects than the aromatase inhibitors.

In January of this year, for the first time an oral SERD got approved. Elacestrant is the name of that drug, commercially known as Orserdu. So that's the first oral SERD to get approved. And it's specifically approved for breast cancer that has mutation in the ESR1. That's a protein inside the cell. It's an acquired mutation, and it accounts for most of the resistance to endocrine therapy in metastatic breast cancer. So metastatic breast cancer that has progressed on first-line treatment and has this mutation, those patients can now be treated with this oral SERD.

There are a whole number of other oral SERDs that are in development with different drug companies, and many of them are now being looked at and evaluated in the early stage adjuvant setting. So that's going to be exciting. Maybe they'll even decrease the risk of recurrence even further than what we get with the drugs that we already have.

Before -- I want to get to one topic that's very important to many of you, and that is the duration of endocrine therapy in the adjuvant setting. How long should we -- in the early stage breast cancer setting, patients who've had surgery, how long should we continue the endocrine therapy to decrease the risk of recurrence? Well, the standard practice is a minimum of 5 years. And there's some data, some studies now, a group of different studies which show that extended treatment to 10 years can be beneficial. It can decrease the rates of recurrence and possibly, unclear -- not totally clear whether it affects overall survival, but definitely decreases risk of recurrence. So we consider extended treatment to 10 years appropriate in higher risk patients.

So how do we decide who we should give the longer therapy? The longer therapy we call extended adjuvant therapy. Well, first of all, again, I just want to go back to the rationale for extended adjuvant endocrine therapy. The rationale is for hormone receptor-negative breast cancer, if a patient is going to recur, it's likely she will recur in the first three to five years following diagnosis. If she hasn't recurred by then, then it's unlikely she will recur at all. However, in contrast, breast cancer that is hormone receptor-positive continues to have risk of recurrence, extending up to 25 years after the diagnosis and maybe even a little beyond that. And as I said, extending treatment for up to 10 years has been shown to decrease risks of recurrence and possibly improve even overall survival.

So I will say, extended adjuvant endocrine therapy or endocrine therapy beyond 5 years is an option for all patients with hormone receptor-positive breast cancer. But some patients are more likely than other patients to derive benefit from the continuation of endocrine therapy. And the continuation of therapy does have side effects. We talked about all the other side effects of the treatment, including decrease in bone density, increased risk of blood clot, increased risk of uterine cancer with tamoxifen. So all those risks do increase with time.

So how do we decide who we should extend the adjuvant endocrine therapy in? Well, I think for women, the risk of recurrence, as I said, it is continuous after stopping the drug. But the risk of recurrence strongly correlates with lymph node status. So patients with higher numbers of lymph nodes, positive lymph nodes are at greater risk than patients with lower number of lymph node involvement or who have negative lymph nodes. Tumor size is a risk factor. The higher the tumor size or greater the tumor size, the higher the risk of recurrence. And tumor grade. Poorly differentiated or high-grade tumors are more likely to recur than lower grade tumors.

So I would say for women with larger tumors or node-positive disease, I suggest extended adjuvant endocrine therapy if the woman can tolerate the endocrine therapy and there are no contraindications. For women with smaller lymph node-negative tumors, the benefits are less clear. And we really have to individualize the treatment decision for those patients with those smaller tumors, lymph node-negative tumors, how much the benefit of added protection is worth it to them, how they're tolerating the drug thus far. We have to really individualize the decision, and it's a long discussion with the patients.

There is a genomic -- there are two genomic tests that can help us make the decision. One genomic test is the Breast Cancer Index. That is a test which gives us two pieces of information. So it's a genomic test performed on the original tumor. So we have to recover the original tumor. And the two pieces of information it gives us, it looks at the DNA expression of a handful of genes that they assay the expression of it, and then they give us two pieces of information. Number one is whether or not an additional 5 years so anti-estrogen therapy is likely to decrease the risk of recurrence in that particular case, in that patient's tumor. And there we get a yes/no answer. And number two, they give an individualized risk of recurrence between years 5 and 10 based on the original tumor biology for a particular patient.

So we have the risk of recurrence for years 5 to 10 from this test and whether or not treatment is going to -- is predicted to have benefit during that time. So you could have a patient who has a high risk of recurrence, but the test predicts that there's no additional benefit beyond 5 years with endocrine therapy. So there, unfortunately, even though the patient has a high risk of recurrence, it indicates there's no benefit, and we may stop the drug at 5 years. Whereas if you have a patient who has high risk of recurrence, or even an intermediate risk of recurrence but is predicted to have benefit for the additional 5 years of treatment, that patient may opt for additional treatment. Again, individualizing it, and perhaps we could use this genomic assay to help us. Often when we give the data to the patient from the genomic assay, it can help them make a decision one way or the other.

One other test that also has been helpful and has some data showing that it can be helpful in predicting whether or not there is a benefit for additional endocrine therapy is the MammaPrint assay, which is the 70 gene assay. That can have some predictive value in terms of the benefit of extended adjuvant therapy. But the Oncotype test, that test which we use when a patient is first diagnosed, it's a genomic assay on the tumor, and that test can predict whether chemotherapy's a benefit in a particular patient, but it doesn't help predict whether extending adjuvant endocrine therapy is a benefit.

I thank you for your attention and can take your questions now.

Robin Perlmutter: Thank you.

Unidentified Participant: Dr. Green, how do you help younger women balance -- for decision-making purposes, balance the long-term risk of using an endocrine therapy against the uncertainty of long-term survival? And I'm thinking in terms of bone health, especially starting at a younger age, of the compromised bone health, cholesterol, the other side effects that you mentioned.

Dr. Karen B. Green: Yeah. So I actually ended up skipping, because of time constraints, skipping my slide on bone health. So monitoring bone health, as you brought up, is very important. I get baseline bone densities. If they are low, I have a low threshold for using bone modifying agents. There's one agent, zoledronic acid, or Zometa. That agent, when given, that's an infusion. It's in the same class of drugs as Fosamax, a commonly used drug. It's in the class of drugs called bisphosphonate. Zometa given twice a year has been shown to further decrease the risk of spread of breast cancer to the bone. So I have a low threshold for using that medicine in women who have low bone density.

So I have, for instance, a woman who had pregnancy-associated breast cancer. She had her adjuvant chemotherapy and anti-HER2 therapy. And we decided in her case to use ovarian function suppression and an AI, aromatase inhibitor. And I got a baseline bone density, and she had osteoporosis, lo and behold, much to our surprise, because she's only in her 30s. So we have her on Zometa to both help -- it's a treatment for low bone density. It's the same medication that's used in Reclast, a treatment for osteoporosis. And it also further decreases the risk of spread to the bone.

But it's definitely a tricky balance. We have to follow cholesterol levels, as you mentioned. We try to focus on diet, healthy diet and exercise to help modify those factors that can help with cholesterol. And exercise can help with bone health as well. So we really have to kind of individualize. It's a lot of discussion. Again, it also depends how risky a particular patient's breast cancer is. How big her tumor is, how aggressive the cancer is, whether or not there are lymph nodes involved and the extent of lymph node involvement. And it's really, it's a long discussion, and it's really individualized. And it's tricky. I do worry about the long-term health, and we try to modify as many factors as we can to keep the patient healthy.

Unidentified Participant: Thank you.

Robin Perlmutter: Okay. Next question. Okay. Dr. Green, do AIs increase the risk of dementia due to the lack of estrogen?

Dr. Karen B. Green: I don't -- it's not reported. It's not reported. Women do know a little bit of some women, a little bit of let's say at their job, forgetting things a little bit. But I don't think that there's an outright increase in dementia risk.

Robin Perlmutter: Okay. Thank you. Someone's writing in that they're triple positive, and they want to know your thoughts on an oophorectomy versus ovary medication and would this decrease their chance of recurrence.

Dr. Karen B. Green: So, I have not been using a lot of -- for Stage 1 HER2-positive breast cancer, the results, long-term disease-free and overall survival results are so high with just adjuvant tamoxifen and Herceptin that

I haven't been using ovarian function suppression and AI in those patients because those breast cancers are so sensitive to the anti-HER2 effect of the Herceptin. However, patients who have a lot of nodal involvement, then I would use ovarian -- who have nodal involvement, then I would use ovarian suppression and an AI.

I generally don't use ovarian suppression and tamoxifen. If I'm going to go to the extent of using ovarian suppression, I generally use an AI with it. Because to me, if I'm going that far to give them the side effects of menopause, I would also want to give them every chance. And OFS plus AI is a little superior than OFS plus tamoxifen, and both are superior than tamoxifen alone. But again, I only reserve -- I reserve the OFS and AI or tamoxifen for high-risk women.

And regarding oophorectomy versus medications, I would not take anyone directly to an oophorectomy unless they had a known ovarian cancer-causing mutation, like a BRCA1 or BRCA2 gene. Because some patients find it's a big adjustment going into an abrupt menopause. So I like to give the medications first to see how a patient tolerates menopause. And if they tolerate menopause and they're doing fine, then we can consider the oophorectomy, and they don't have to come in for the monthly injections. And we have more complete and definitive ovarian and more complete definitive estrogen suppression. But first, I generally use medication first.

Robin Perlmutter: Thank you. So I have another question. You mentioned that carpal tunnel is a side effect of anastrozole. And if you've been on anastrozole since August and have mild carpal tunnel, could it be the drug?

Dr. Karen B. Green: It certainly could be the drug. One can stop it, interrupt therapy for a few weeks and see if it gets better. I just recently went through this with one of my patients. She had carpal tunnel, and we interrupted her therapy, and she said she felt better. She was on anastrozole. Then we switched her to letrozole. I'm meeting with her tomorrow. I think she's actually starting to get symptoms again.

But other things we can do for the carpal tunnel are we can have them see a hand surgeon. They can get steroid -- wrist splints are enough to help some patients. Steroid injections can help. And a minor surgery can help, what's called carpal tunnel release. It's an easy surgery and a quick recovery, and that can take away that issue if that's the one issue that's preventing use of a good drug.

Robin Perlmutter: Okay. This is going to be our last question. It's someone asking if you can address a little bit more, and maybe it would be helpful for the woman who did type this question, if you could be a little more specific. She wants to know more about the 5 to 10 years use of the aromatase medications with high-grade, Stage 2 breast cancer. So that's getting a little specific, but I don't know if there's something you can add to on the use of those drugs for 5 or 10 years.

Dr. Karen B. Green: So that's for lymph node positive?

Robin Perlmutter: It doesn't say. It's just a high grade.

Dr. Karen B. Green: If it's a large tumor and/or lymph node positive, I would favor 10 years if the particular individual can tolerate the side effects. There are some patients I've gotten up to 5 years with some patients,

and they say, I have had enough. I cannot do this anymore. And those -- they elect to stop. Most of those patients will be fine. We are preventing only a small number of recurrences, but we are preventing some recurrences. So it's, again, an individualized discussion.

I will comment also, there was one study that showed -- it took patients who had received 5 years of the AI and randomized them to 2.5 more years or 5 more years. So patients got a total of either 7.5 or 10 years of therapy. And there wasn't much of a difference between the 10 years versus 7.5 years. So it's possible that 7.5 years of therapy is a sweet spot. For some of my patients who were kind of on the border, I might say, let's try to just get to 7 years and stop there, especially the ones who are lymph node negative.

Robin Perlmutter: Okay. Well, thank you very much. And folks, that's the end of our presentation for tonight. And I want to take this opportunity to thank Dr. Green for her fantastic presentation. Very comprehensive. For your passion, dedication and commitment to the cancer community. And to all of you for coming out tonight and participating. Have a great night, everyone.

DR. Karen B. Green: Thank you. Have a good night. Thank you.