[MUSIC PLAYING]

SPEAKER 1: I'm going to talk today about endocrine therapy, too much of a good thing? So we know that breast cancer is one of the most common cancers that we encounter in women. And with that, about 2/3 of all breast cancer are estrogen receptor-positive. And I know that Dr. Appleman tried to take credit for targeted therapy in prostate cancer with androgen deprivation. But we'd like to think in breast cancer that this was kind of the first success story of targeted therapy.

Here's my token historical slide. But this is from 1896. Beat that. But ultimately, this was looking at the novel treatment of oophorectomy to treat breast cancer. And this was kind of back before we knew that breast cancer was different, whether you were pre or post-menopausal, and back before we knew that there was such a thing as the estrogen receptor, and the estrogen receptor was influenced by hormone therapy.

But kind of a very interesting story, George Beatson, was a Scottish surgeon. And during his thesis he lived near a sheep farm. And he kind of noticed that sheep who underwent oophorectomy had different changes in their breast tissue and that the proliferating, lactating kind of sheep breast tissue was similar to what you saw in breast cancer-- so, very interesting.

And if you kind of look at the pros, as well, I think it's kind of very lovely writing. And apparently, that's something he was known for, as well, to have kind of a very lovely way of expressing his thoughts-- but ultimately, again, 1896. Now a little slow in breast cancer, so even though we've known about this idea of ovarian suppression for over 100 years, we actually didn't quite realize who really needed it and who would benefit from ovarian suppression until about three years ago.

But with that, I think what we've learned over time, and what we do in the modern era with breast cancer in terms of hormone therapy, is really kind of thinking it differently. So this idea of subset analysis, we'll come back to in breast cancer. Because a lot of things, I think, while you can kind of statistically argue that you're slicing the data in a way to look at it, I think it's probably a little bit limited to think of all of breast cancer as one disease or all of cancer as one disease. And you really need to think of it in these subsets of disease.

But ultimately, just in terms of where we are, if someone is pre-menopausal and has estrogen receptor-positive breast cancer, our primary therapy is a drug called tamoxifen, which is also an old drug that's been around for a long time. In some cases, we will consider ovarian suppression, as well. And this is really the people who we consider to be at highest risk, so women diagnosed before age 35, women with node positive disease, and women who chemotherapy doesn't put into menopause, which is actually part of the benefit of chemotherapy.

But ultimately, sometimes we give it with tamoxifen. Probably the best data is supporting giving ovarian suppression in combination with aromatase inhibitor. But many women will do fine with tamoxifen alone. On the other hand, we have women who are post-menopausal at the time of their breast cancer diagnosis.

And really, the preferred treatment in that patient population are the aromatase inhibitor drugs. And I've listed them here for you. But these are drugs like anastrozole-- the other name for that is Arimidex-- exemestane, letrozole, or Femara. But sometimes we'll consider the use of tamoxifen, as well.

So tamoxifen is a drug that works as a partial agonist antagonist. So we also call this a SERM, a Selective Estrogen Receptor Modulator. Again, because it works at the level of the estrogen receptor, it has efficacy in both pre and post-menopausal women. But on average, there is benefit to this drug, about a 40% reduction in the risk of breast cancer recurrence, which is probably the endpoint that we find to be most meaningful, as well as about a 34% reduction in the risk of death, which is a little bit more complicated, as we've seen in the prostate cancer literature.

And historically, we've given this for five years. So the reason why we gave it for five years is a little bit nebulous. But ultimately, studies looked at one year. Studies looked at three years. Studies looked at five years.

And five years kind of settled out as being the winner. So when you look at, in terms of both recurrence and mortality, there is benefit over no treatment to give tamoxifen. And this was looked at in a number of individual studies, and ultimately, summarized in a large analysis done by the Breast Cancer Trialists' Cooperative Group.

Aromatase inhibitors, on the other hand, these drugs work by inhibiting peripheral conversion of androgens to estradiol. So a couple of important points-- because we get we talk about this all the time with our patients-- is that the tissue levels of estrogen are not the same as circulating levels of estrogen, kind of two different things. The other of which is that the highest concentration of aromatase in someone's body is actually in the female breast. So the breast really self-selects for this high estrogen environment.

But ultimately, these drugs help to reduce those estrogen levels. So compared to tamoxifen-- we'll talk about this briefly-- these are more effective, relatively speaking, a safer side effect profile. With tamoxifen, we worry about blood clots, stroke, and uterine cancer, which we don't see with the AIs. But they have their own whole separate set of side effects. And historically, these have been given for five years.

So a number of questions have existed in endocrine therapy for breast cancer. The first is, who gets it? And that's relatively simple to answer. Our guidelines say, anyone who is at least 1% estrogen receptor-positive should be considered. Why do we give it? Arguably, kind of the best treatment we have for breast cancer, particularly for those who are hormone receptor-positive-- and in many cases, the efficacy that you see with endocrine therapy much outweighs the benefit that you see with chemotherapy.

And then, really, the last question we've had is, how long do you give it for? Do you give it forever? Do you give it for five years? Do you give it for 10 years? Or does it depend?

So why do we even worry about this? And this was some data that was presented at our national meeting the American Society of Clinical Oncology this year. And it was really kind of something that highlighted what we had thought as oncologists but was really pretty sobering data. And this is another thing that we get asked all the time in clinic, as well, is, well, aren't patients cured after five years? Isn't there kind of this magical thing that happens at five years where breast cancer doesn't come back any more?

And the answer to that, unfortunately, is, no, five years doesn't mean anything in estrogen receptor-positive breast cancer-- and maybe triple negative breast cancer, but certainly not estrogen-positive positive. But this data that was presented showed-- really graphically, as you can see-- that the risk of recurrence continues to increase over time. So when you started kind of this magical five-year mark, which isn't so magical, unfortunately, after all, the risk of recurrence continues to increase over time. And perhaps, in someone who has a small node negative tumor, that might be 14% at 20 years. That may be as high as 47% at 20 years for someone who has a bigger node positive cancer.

And if you look at when patients recur, over half of the recurrences happen after year five. So again, this five-year mark doesn't mean anything. But it's kind of helped to support this idea of continuing therapy longer. So are people recurring after you stop the treatment because the treatment is suppressing the recurrence to some extent?

So with this, when we think about breast cancer, particularly estrogen positive breast cancer, we need to think of it in terms of a 20-year perspective. And if you look at women who would die of nothing else but breast cancer, 80% would live to age 80 if there was no risk of death from breast cancer. So it is something that is important.

However, when you stop the treatment at five years, you expect these recurrences to steadily increase. And again, there's not a single patient population where that risk decreases. And for every patient population, unfortunately, that risk continues to slowly increase over time.

So what we knew prior to 2016 was that, in the case of tamoxifen, if you continued tamoxifen for 10 years, that was, in fact, beneficial compared to tamoxifen for five years. And when we look at the absolute benefit in prostate cancer, this wasn't too exciting. But in breast cancer, this was actually statistically significant, in terms of the absolute benefit. But the absolute benefit was about 4% in two separate studies. They then combined analysis from these two separate studies with nearly 10,000 patients and were able to show that, for everyone, 10 years was better than five years.

Questions remain. And those questions are, is this truly because you're taking the medicine for longer? Is it something to do with the efficacy of tamoxifen-- and that may be different with the aromatase inhibitors?

Is this something inherently different between pre-menopausal women versus post-menopausal women? So this led to an update of our national guidelines, the ASCO guidelines, for hormone receptor-positive breast cancer to say, if a woman starts out pre or perimenopausal and they've had five years of TAM, you can offer them 10 years. If they've started out pre or perimenopausal, became post-menopausal, and finished five years of TAM, then you can get them five years of aromatase inhibitor as an alternative.

So we also knew-- and just kind of focusing now on post-menopausal women-- we knew that, if you were to compare five years of tamoxifen to five years of AI-- and I'm not expecting you to see this. I think this is just really highlighting the fact that, again, we've like duplicity in oncology. And there were a number of studies from a number of different sites that all showed the same thing, that compared to tamoxifen, aromatase inhibitors performed a little bit better. And a little bit better is about 2% to 4% better than tamoxifen.

We thought that, well, maybe it's because of side effects that that also favors the aromatase inhibitor. And then there was also some data that said that, if you started out with tamoxifen, you could switch to AI. If you started out with AI, you could switch to tamoxifen, and it was just as good as AI for five years. So this is where we were up until just very recently.

So what started kind of this idea about extended aromatase inhibitor is we knew that after five years of TAM was helpful. There were a couple of studies published probably about 10 years ago now for patients who happened to get five years of TAM and then the aromatase inhibitors came out if they got five years of aromatase inhibitor. And there was benefit to that, too. So we had these studies that were accumulating that said that maybe 10 years was, in fact, better than five years.

So what about extended AI? So this brings us to the question at hand. What about five more years of aromatase inhibitor after your initial five years? And actually, many of these slides I borrowed from Barry Lembersky. But this one, I've distinctly given him credit for. But ultimately, this was a side that we talked about in our recent local San Antonio review where we talk about the most important presentations at that meeting.

And really, patients fall into one of three camps after their five years of AI. It's, I can't stand this stuff. I can't wait to get off of it. I did my penance of five years. I never want to take it again.

I never want to stop it, because this is my lifeline. This is what I think is keeping me healthy. And then the third kind of patient population is, well, what do you think I should do?

So this year, again, in 2016, two really important maybe practice-changing studies were reported, the first of which was reported at our June meeting, which is the ASCO meeting, the second of which was reported at our December meeting, the San Antonio Breast Cancer Symposium. So the first was, again, presented at ASCO and subsequently published in *The New England Journal,* looking at five years of letrozole all after five years of AI with some degree of tamoxifen ahead of time, so a pretty motivated patient population. Just keep that in mind when you're looking at this data.

So in MA.17, that was one of those studies that showed benefit of five years of AI after five years of TAM. So in that study, patients actually got a secondary randomization to say, you've done some amount of tamoxifen. You've done five years of AI. We're going to re-randomize you to either an additional five years of letrozole or placebo-- so all hormone receptor-positive, obviously, all postmenopausal, all no evidence of disease.

So again, did the 10 years do better than five years? In this study, the primary objective was disease-free survival. And note the way that disease-free survival was defined. It was defined as time to recurrence, so recurrence of the current breast cancer, or time to development of a contralateral breast cancer, whichever comes first. And again, this is kind of one of those things that, when you're looking at the literature, understanding the similarities and differences between the patient populations and the definitions, which you think should be consistent, aren't always-- also, number of secondary objectives.

And then, importantly-- I think this is something to keep in mind when you're looking at potential bone effects of these agents-- but over 70% of patients on each arm had had nearly five years of tamoxifen. So we think of two months if it is being bone-protective. Also importantly, about half the patients were lymph-node positive. About half had gotten chemotherapy.

So in terms of the primary endpoint, the five-year disease-free survival was 95% with letrozole compared to 91% with placebo. This hazard ratio was 0.66. This was statistically significant.

But the next thing to look at is, what made up those events? So when you look at distant recurrence-- which, as medical oncologists, we worry about patients becoming metastatic. The distance recurrence rate was relatively similar, 4.4% in letrozole compared to 5.5% with placebo.

Where you really started to see the advantage of the extended endocrine therapy was in terms of new contralateral breast cancers. And you can see these numbers are small. And we think about the survival we were seeing with prostate cancer, the magnitude of benefit with prostate cancer, these are tiny numbers. But when you apply these tiny numbers to large populations of people, there is some benefit there. So while nobody wants to have breast cancer twice, if you have a second breast cancer that can then be cured, it's a much different scenario than having a metastatic recurrence of your first cancer.

So ultimately, this was felt to be a success. And this success was, OK, 10 years is better than five. The overall endpoint was improved. You had to have a discussion with patients to say, well, probably the biggest magnitude of benefit is prevention of the second cancer. But this was a discussion that we were having in our clinics between June and December.

So what about side effects? So overall, relatively well-tolerated-- again, remember, this is a very compliant group of patients who had now been on some type of therapy for 15 years. There was more bone pain, as you would expect, with the letrozole, a little bit more elevated alkaline phosphatase, more elevated liver enzyme, actually, with placebo. But the major thing that we worry about is fracture and osteoporosis, which was, in fact, worse with the extended AI-- these patients had already had tamoxifen-- but not huge numbers, in about what we think about 10%.

So the conclusion of this was a 34% reduction in any disease recurrence. The absolute benefit, in terms of prevention of metastasis, was only about 1%. This reduction in contralateral breast cancer really tended to drive the benefit. There was no difference in overall survival, so very different than the numbers we were looking at in prostate cancer, 93% letrozole, 94% placebo, not statistically different subset analysis, didn't show a group in this study that appeared to benefit more. And then the bone health is, obviously, a huge issue.

So at the same meeting, they looked at quality of life. So what happened to patients? So it's one thing to look at metastasis. It's one thing to look at contralateral breast cancer. Those numbers are all small. So how did patients feel?

And they looked at a number of kind of standard measures of quality of life. Importantly, most patients were pretty compliant with questionnaire filling out, about 85%, which is kind of amazing if you think about it. But ultimately, there was no difference in global quality of life. So that was important.

So even though patients continued on longer, they didn't feel any worse. And importantly, as well, the quality of life was similar to the average post-menopausal woman. And there was no difference, in terms of age, so difference in younger post-menopausal women versus older post-menopausal women.

So now this brings us to December of 2016. In December of 2016, the second large study was presented looking at 10 years versus five years. So this was NSABP B-42. A couple of names I have underlined are local people here in Pittsburgh at Pitt, who were very instrumental to this clinical trial. And they wanted to see, did this improve disease-free survival?

So on the surface, the same endpoint as the study we just looked at-- and these were all, again, post-menopausal, stage 1, 2, or 3A, disease-free after five years. Some patients had had AI for five years. Some who had TAM for less than five years and then switched to AI for the remainder of five years. No one had had, like in MA-17R, where they had had the full five years of tamoxifen first. And again, that randomisation was letrozole versus placebo.

Now the way that disease-free survival was defined in this study was local, regional, or distant recurrence-- OK, so similar to the first study-- contralateral breast cancer-- similar-- second non-breast cancer-- so that one was different-- and death from any cause. Because again, if the therapy's toxic and you're dying from the not recurring of cancer, that's not necessarily helpful. And then the other kind of important point is you always think of a p-value as less than 0.5 as being statistically significant. In this study, they had to spend alpha, which was kind of a new concept for me.

But ultimately, they had four preplanned analyzes. And with that, that spent some of the alpha that they had available, as far as the statistical significance. So what was statistically significant in this study was a p-value of 0.418.

So in terms of similarities and differences from the previous study we looked at, a little bit more were node-negative. Only about 40% had received prior tamoxifen, because maybe it's a 15-year treatment, not a 10-year treatment compared to a five-year treatment. And in this study, in terms of compliance, about 60% of patients were compliant. In the other study, about 80% of patients were compliant.

So in terms of the primary endpoint of disease-free survival, the hazard ratio here was 0.885. The p-value was 0.048. However, this did not reach statistical significance. So this was felt to be negative for the primary endpoint. When you looked at subgroups, there wasn't a specific subgroup that stood out as reporting or explaining where the benefit was.

And then let's look at these events that we find to be not desirable. So the first undesirable event for patients is a breast cancer event. So this is, what's the chance that you'll have something related to breast cancer again? And you do see that this is different. So the incidence of that was 6.7% with letrozole, compared to 10% with placebo. This did show some statistical significance.

The other event that we don't like to see is distant recurrence. And in this study, kind of contra to the first study we looked at, this actually did show a benefit, in terms of decreased distant recurrence with letrozole, compared to placebo. And then in overall survival, again, no different. Although, sometimes, again, when we think of breast cancer as a 20-year disease, we might not see these overall survival events happen for another five years.

In terms of side effects, there was a higher incidence of fracture numerically. However, this was not significant. So that was important to note.

Interestingly, there was this look at arterial thrombotic events. And it was interesting in the sense that it was lower while you were on treatment. When treatment was stopped, then that flipped.

You can see the dashed line versus the solid line that that changed. So there was a difference there. It's hard to know what to make of that.

So when this study was presented, these were the conclusions. The conclusions were that it did not reach statistical significance. There was no difference in overall survival. There was, however, a statistically significant improvement in breast cancer-free interval, 29% reduction in a second breast event, whether that was a recurrence or a second cancer, statistically significant reduction in the rate of distant recurrence, 28% reduction. There was no increased risk of fracture, which was different than what we had seen in MA-17R, and then this risk of arterial thrombotic event.

So what was kind of very aptly noted by the investigator that had presented this study was that they actually had different definitions of disease-free survival. And when you look at the data, giving them both the same definition of disease-free survival, it technically wasn't significant in either study. However, the breast cancer-free interval, which is recurrence or second breast event, was significant in both study. And the magnitude of benefit was pretty similar with the two of those.

So really, you kind of think, well, what's going on here? And what do you do in the clinic? And just like every other disease that you're learning about, there are other things that influence response to treatment. And those are typically genetic influences and environmental influences.

And there is some data looking at this. Because again, it's not just one disease. And that's where I maybe kind of argue that it is important to look at subset analysis. Because this is really where you tend to tease out the differences in patients.

This was also presented at San Antonio this year. And it looked at these different signatures that are available in a large cohort of patients for whom tissue and outcome were available. And ultimately, they looked at a number of different assays. If you've ever been to our cancer clinics, we talk about things like MammaPrint, and Oncotype, and BCI, and some of these commercially-available genomic assays that help to predict what someone's outcome will be and what someone's potential benefit from chemo would be.

But the question they looked at here was slightly different is to compare these to each other in this group of patients, and then to look specifically at late recurrence. So could you predict who may have a late recurrence? And then could you predict who was potentially more likely to benefit from extended therapy?

And what they found is that there were, in fact, prognostic endpoints that you could detect from these different assays. And interestingly, it was a little bit different between node-negative and node-positive. But both were able to identify a group for whom extended endocrine therapy wasn't justified.

So if you're thinking about if somebody is miserable on their AIs, in terms of joint pain, if somebody has developed osteoporosis and can't take a bisphosphonate, then maybe you could identify a really low-risk group of patients. So with this, we have this genomic bake-off, as we've called it. So that B42 study, there's 3,000 tumor blocks available. And out of those 3,000 tumor blocks, there are 195 distant recurrences. So all of these different assays will be looked at to say, at the time of diagnosis, can you predict what somebody should be doing in five years or in 10 years?

So this is data that we'll be anxiously awaiting. The other thing, in terms of the environment-- this is kind of the patient's own microenvironment-- there are some factors that predict benefit of treatment. In this ABCSG-- I didn't go into it-- it was a similar Austrian study looking at 10 years versus five years, relatively similar data to the others. What I want you to notice is that those patients who are normal body weight appear to benefit more from extended AI than those patients who are overweight or obese, which we know is a risk factor for recurrence, have less benefit from extended AI. So it's probably not going to be this very simple, final answer of we have a 10,000 patient study to say yes or no for everybody. There's probably, again, going to be these nuances, both with the genomic factors of the tumor, the patient, and their microenvironment, or their larger environment, and then kind of, again, looking at what the data tells us.

So what do we do? So I think it's important to consider, which patients are really at risk? The short answer is, it's probably everyone. Although, there's different degrees to which patients are at risk. I think it's going to be important to continue to consider genomic factors within the tumor that can predict late recurrence. And then how can we balance the bone health issues?

And it was interesting, because at the first meeting where the MA-17 was presented, the discussant actually said, well, we should just give bisphosphonates to everybody. That would help everything. And there are some people who, again, kind of have these debates where they say, yeah, that's a great idea, versus not. We didn't shave someone's head at the podium, but it was relatively similarly contentious discussions.

So this is where I think we are, so the conclusions at this time. And I think, like anything else, like you heard from Dr. Appleman, it's different. And its patient-specific. So who do we think about 10 years?

So 10 years is probably people who did great the first five. If you're tolerating the medicine well, you're not having a lot of side effects, it's important to be upfront about what those benefits are, maybe around 5%. Although, we do a lot in breast cancer for 2% to 5% benefit.

People who have good bone health, that's an important group. Women who are younger-- so if you have an 85-year-old who you're looking at five more years of AI, it's going to be different than a 60-year-old, where you're looking at five more years of AI. Perhaps, those patients who are node-positive, those higher-risk patients, patients who are more strongly hormone dependent, in terms of their signaling. So it's not going to be your ER 10%. It's going to be your ER 90%.

And then, perhaps, maybe in the next five years, we'll be able to tell from a genomic assay who we should continue. And then people who you think it's probably OK to come off are going to be those who are suffering, those who have issues with their bone density, those who are low-risk. And again, we think we can predict low risk. We probably can't predict it as well as we think. But maybe you can do it more from kind of an unbiased genomic assay.