



354 West Lancaster Avenue | Suite 224 | Haverford, PA 19041

Phone: (610) 645-4567

Fax: (610) 645-4573

Survivors' Helpline: (888) 753-LBBC (5222)

LIVING
BEYOND
BREAST
CANCER®
L B B C . O R G

What's New? Breaking News from the 31st Annual San Antonio Breast Cancer Symposium

January 26, 2009
Kathy D. Miller, MD

ELYSE S. CAPLAN, MA:

Welcome, everyone ... Today's program highlights some of the latest research that was presented last month in San Antonio, which many of you know is the largest international meeting of breast cancer researchers, clinicians, scientists and patient advocates.

We're very much looking forward to hearing the latest treatment information that relates to early stage breast cancer or adjuvant treatment for hormone receptor-positive and negative breast cancer, and also [to information on] the studies that highlighted developments in the metastatic breast cancer arena, again also utilizing a hormone therapy, as well as other forms of chemotherapy.

My name is Elyse Caplan. I'm the education director here at Living Beyond Breast Cancer [<http://www.lbbc.org>]. I'm very happy to moderate today's program.

We need to acknowledge the generous support from Genentech that helped make today's teleconference possible ... [another] key point that you may learn about today [pertains to] communicating with your doctor about some of the questions that you may want to ask [in regard to] your treatment plan moving forward.

I'd like to tell you a little bit about our featured speaker today, Dr. Kathy Miller. Dr. Miller is an associate professor and Sheila D. Ward scholar at Indiana University Melvin and Bren Simon Cancer Center [<http://cancer.iu.edu/>]. She's a member of Living Beyond Breast Cancer's medical advisory board as well, and she has authored more than 60 scientific papers, many focusing on breast cancer biology and treatment.

Dr. Miller has served as co-chair of the Hoosier Oncology Group Breast Cancer Committee [<http://www.hoosieroncologygroup.org>] since early 2002, and she has honed her ability to coordinate multicenter trials as principal investigator for E2100, which is a phase III trial to confirm the benefits of antiangiogenic therapy

in women with metastatic breast cancer. Dr. Miller is also working with the Eastern Cooperative Oncology Group [<http://ecog.dfci.harvard.edu/>] to bring antiangiogenic therapy to the early stage setting.

There are so many more credits to Dr. Miller's name but, without further delay, please welcome Dr. Kathy Miller.

KATHY D. MILLER, MD:

Thank you, Elyse. And thank you all for joining me. We'll first talk about new developments in the adjuvant therapy of patients newly diagnosed, thinking first about hormonal therapy treatments for patients whose tumors are hormone sensitive, and then thinking about trials that might help us further define the optimal chemotherapy regimens. We'll then shift our thinking to those patients with more advanced or metastatic disease, first [discussing] hormone therapy in patients with HER2 positive disease, then focusing on a couple of abstracts that deal with chemotherapy in the metastatic setting.

[In terms of] hormone therapy in the adjuvant setting, there really have been two major innovations or changes in the last five or six years. The first of those has been an increased use of the aromatase inhibitors – drugs like anastrozole, or Arimidex, or Femara or Aromasin – for postmenopausal patients; [the second is] the use of a genetic test, called the Oncotype DX Recurrence Score Assay, to help us identify which patients whose tumors are estrogen sensitive and don't involve the lymph nodes might have a higher risk of recurrence and might need chemotherapy and which patients might safely be treated with hormone therapy alone. Those two innovations were brought together in an analysis of the ATAC trial, which was one of the large trials that looked at the aromatase inhibitors compared to tamoxifen and that used the Oncotype DX Recurrence Score Assay on the samples collected from those patients.

It's important that we think first about these two issues individually. The Oncotype DX Recurrence Score Assay evaluates 21 different genes that are expressed in breast cancer. They're expressed to different degrees. These are not genes that are inherited or passed in families. They're simply things that all breast cancers have, but in very different amounts. It gives a score of anywhere from zero to 100. Patients who have lower scores have a lower risk of recurrence if they're treated with tamoxifen compared to patients who have higher scores. And patients who have scores in what we've defined as the high-risk range derive a very large benefit from the addition of chemotherapy. Patients who have scores in the low-risk range probably don't require chemotherapy and don't get any benefit.

One of the criticisms of this test and how it was developed is that it only looked at the benefit of tamoxifen. As more postmenopausal women are treated with the aromatase inhibitor, it is, I think, an important and legitimate question: would this test perform as well – be as predictive – if we used a different hormone therapy? The other criticism was that these were patients [who were] treated now more than 15 years ago, and a lot has changed in the diagnosis of breast cancer; in the standards of treatment. It would be nice to know [whether or not] it's just as predictive in patients who are treated in a more contemporary time.

That ATAC trial was the first of the trials to look at the role of the aromatase inhibitors in early stage treatment. It specifically looked at anastrozole – Arimidex – [versus] tamoxifen. And then there was a third group that looked at both of those two hormone therapies combined. This was the first trial to show that the aromatase inhibitors [resulted in] an improvement in disease-free survival compared to tamoxifen. Those patients have now been followed for not quite 10 years, but we have at least seven to nine years of follow-up on most of those patients. They were able to go back and



do the Oncotype DX Recurrence Score Assay on a subset of the samples from those patients to see if it was equally predictive. The good news for everyone is that the tests performed equally well in patients who were randomized to receive the aromatase inhibitor as in patients who were randomized to receive tamoxifen.

It also added to the prognostic information that we got from other staging information. My surgeons have frequently wondered if, with this test, we're saying that tumor size and lymph node status don't matter anymore. That's absolutely not the case. Patients who had larger tumors were at higher risk of recurrence within each Oncotype DX score. The involvement of nodes increased the risk of recurrence within each Oncotype DX score. So [the Oncotype DX test and the results of other diagnostic tests] added to information of each other, rather than [Oncotype DX] replacing the other [tests].

There was another important study that looked at the aromatase inhibitors in the adjuvant setting [and] that we all had big hopes for. But, unfortunately, I think we all [were] left feeling a bit let down or disappointed. That study is known as the BIG I-98 study. This was a trial that has gone through several changes throughout its history. It initially had a very simple design that was similar to [that of] the ATAC trial; it was simply going to compare five years of tamoxifen to five years of letrozole, otherwise known as Femara.

But as that trial got started, when it had enrolled about 1,800 patients, we got information from some of the studies that looked at switching from tamoxifen to an aromatase inhibitor after two to three years. And the question of whether [or not] that sequence might be more beneficial became particularly important, so the trial was amended, and they added four additional arms. So there are now patients treated with five years of tamoxifen, patients treated with five years of letrozole and [patients treated with] two different sequences, [with some patients receiving] two years of tamoxifen [followed by] three years of letrozole [and others receiving] two years of letrozole [followed by] three years of tamoxifen.

[In terms of] the results of this trial, life then got further complicated because, as the trial went along, we got information about continuing with an aromatase inhibitor after five years of tamoxifen, [as well as] more information about switching. So, many of the patients in the single-agent tamoxifen arm actually were treated with an

aromatase inhibitor at some point during the analysis. It required a bit of work by the statisticians [in order for them] to be able to give us confidence in the results.

We now have about six to seven years of follow-up on the patients in the two single-agent arms – recall that those arms were begun earlier than the others – and just about five years on patients in this sequential arm. The trial had previously reported that, [in] the single-agent arms – [this is] similar to the ATAC trial – patients who were randomized to letrozole had a lower risk of recurrence. When they looked at switching, [they found] no major differences. Perhaps the patients who had started with two years of tamoxifen and then switched to letrozole had a slightly higher risk of recurrence. That was particularly true for patients who had larger tumors or who had lymph nodes involved – [patients] who were at a higher risk of recurrence to start with. But patients who started with two years of letrozole and then switched to tamoxifen really seemed to do just as well as patients who got five years of letrozole from the very beginning.

In some ways, this made the interpretation and analysis of this trial much more complicated, [given] all of the changes and the differences in treatment throughout the life of this trial. But I think that, certainly, it has confirmed our conclusion that receiving the aromatase inhibitors is very important for patients with ER positive, hormone-sensitive disease who are postmenopausal. And there are still several strategies and timings in which you can do that. I think especially comforting is knowing that the patients who start with an aromatase inhibitor and who then switch to tamoxifen seem to do particularly well. There was no major falloff in the risk of recurrence by making that switch. And I think that should be particularly comforting to women who may start with an aromatase inhibitor and have difficulty, particularly with the musculoskeletal side effects – to know that there is another option, in switching to tamoxifen, that may give them less individual toxicity and that they won't be losing major benefit by taking that opportunity to make another change.

Many of you [know] that there are three aromatase inhibitors [that are] commonly used. We've talked about data [from] the ATAC trial, [which incorporated] anastrozole, and the BIG I-98 trial, [which incorporated] letrozole. Exemestane made the news this year as well, with

the reports of what's known as the TEAM trial. This was exemestane's version of the ATAC trial; initially [it was] designed to be a very simple head-to-head comparison of five years of tamoxifen compared to five years of exemestane. Just like [in] the BIG I-98 trial, as information from other trials became available while this trial was enrolling patients and while they were being followed, it became necessary to let patients in this trial know about those other results and to change the trial.

In particular, the results of a trial that looked at switching from tamoxifen to exemestane after two to three years of tamoxifen led to this trial being changed to comparing five years of exemestane to that switching strategy – two years of tamoxifen followed by two to three years of exemestane. That also resulted in the trial being substantially larger. It was initially going to be about 5,000 patients. It ended up being nearly 10,000 patients to accommodate that change in treatment and the change in the plan along the way.

This, like many trials, was a very large, multinational study. It required patients to have hormone-sensitive disease and to be postmenopausal. They could have had lymph nodes involved or not, and they also could have received chemotherapy or not. Many of the other trials also allowed patients to receive chemotherapy. But because they were predominantly conducted in Europe with lower-stage patients, only a small fraction of those patients [had] received chemotherapy. In the TEAM trial, about a third of the patients had received chemotherapy. And about 45 percent or so of patients had lymph node involvement.

This study looked at both the potential side effects and the benefits of these therapies. Tamoxifen [was associated with] increased risk of vaginal bleeding and problems with uterine, endometrial and vaginal discharge, as well as slightly more hot flashes and slightly more blood clots. When they looked at the musculoskeletal toxicities – [via] reports of achy joints, achy muscles and osteoporosis – [they found that] those were more frequent in patients treated with exemestane. In this study, [for which we] now have about five to seven years of follow-up, there were more recurrences in patients treated with tamoxifen compared to patients treated with exemestane. That was true whether you looked at only about the first two and a half years, before patients switched, or if you looked at the entire population, even after patients had made that switch.



I think this also gives us confidence that, at least [judging by] these studies, there are very few differences in the aromatase inhibitors. There is an ongoing trial directly comparing two of these aromatase inhibitors to let us see if there are any even minor differences in their effectiveness or side effects that might be important. But, at this point, I think women should be much less concerned about which of these aromatase inhibitors they're receiving because their differences are likely to be quite minor, if [they exist] at all.

As we think about hormonal therapy, we also have to think about how these drugs are metabolized. That's particularly important for tamoxifen. [Thanks to] results that we first learned several years ago, [we know that] tamoxifen has to be converted by the body to its most active form. That most active metabolite, or most important conversion, is done by an enzyme in which there are inherited differences. Roughly 7 percent or so of Caucasian women in the United States have inherited a form of that enzyme that just doesn't work as well; [those women's bodies] don't make as much of the active form of the tamoxifen metabolite that's responsible for many of its effects. Those women seem to get fewer side effects. And we have worried that, based on some small analyses of previous trials, perhaps they might also get less benefit from tamoxifen. That has raised questions about whether patients ought to be tested [to determine the] form of this enzyme they've inherited before they start treatment with tamoxifen.

It's also raised questions about the aromatase inhibitor trials; perhaps if we looked at how women metabolize tamoxifen, we might be able to identify a group of women who absolutely are best treated with the aromatase inhibitors and a group of women who, because they metabolize tamoxifen really well – get very high levels of the active metabolite – might actually be better served by treatment with tamoxifen. And, in these large studies that lump everyone together, you simply can't get at that level of detail.

We have the first results of an analysis of a subset of patients in one of those aromatase inhibitor trials. They went back and looked at what form of this metabolizing enzyme [this subset] had inherited, and then they tried to look at whether tamoxifen or the aromatase inhibitor was more effective or was a better choice for those women based on the form of the enzyme they had inherited. The trial they

used was one of the smaller aromatase inhibitor trials, which was known as the ABCSG-8 trial [http://www.abstracts2view.com/sabcs/view.php?nu=SABCS08L_1392&terms=]. This was a trial that randomized women either to five years of tamoxifen or to two years of tamoxifen followed by a planned switch to anastrozole. They went back and looked at a subset of patients in this trial; they did their genotypes and identified patients who were poor metabolizers of tamoxifen, meaning they had inherited one of the metabolizing enzymes that doesn't work very well, so they didn't get much of the active metabolite; extensive metabolizers, who made very high levels of the active metabolite; and patients who were in the middle – women who would be expected to have sort of mid-range levels of the active metabolite.

When they looked at these patients who were treated with tamoxifen, [they discovered that] patients who were the poor metabolizers had a much higher risk of recurrence if they were randomized to tamoxifen compared to those patients who were either extensive metabolizers or intermediate metabolizers. But when they looked at patients who were randomized to switch from tamoxifen to anastrozole, [they found that the form of] enzyme they'd inherited really had no influence on their risk of recurrence at all.

Because this was a smaller study, and because they looked at genotyping only in a subset of patients, [the study] really couldn't tell us whether or not the patients who were extensive metabolizers might actually do better if they were treated with tamoxifen. So this is perhaps a tantalizing hint of things to come rather than information that we can use today. I can tell you that there is a group that has obtained all of the genetic material from one of the larger randomized aromatase inhibitor trials and that is doing the genotyping on all of those patients so that we really will be able to see if treatment with hormone therapy could be individualized in that way for patients in the future.

Our last topic in regard to hormone therapy in the adjuvant setting is [the need] to think a little bit more carefully about bone health. That's particularly important for patients who are treated with the aromatase inhibitors, which have among their potential side effects a risk of increased bone loss and of increased osteoporosis. And we had further results of a trial known as the ZO-FAST trial. This was a trial that enrolled postmenopausal patients with hormone-sensitive disease, all of whom did not have frank osteoporosis at the time

they entered the trial. They were all treated with an aromatase inhibitor; in this trial, the aromatase inhibitor was letrozole. The patients were randomized either to immediate use of zoledronic acid, or Zometa, which is one of the commonly used bisphosphonates for treatment of osteoporosis, or to a delayed use of the zoledronic acid, [in which] induction of that therapy [was] triggered by a significant decrease in bone mineral density, [as identified via] regular bone mineral density testing, or by the development of a fracture. Those patients have been followed for breast cancer recurrence, overall health and bone health.

We saw some of the earlier results of this trial a year or two ago. We know that patients who were in the delayed group had more significant bone loss in the first [three years] of therapy. They lost nearly 5 percent of their bone density in the spine and about 3.5 percent of their bone density in the hip in the first ... [three years], compared to a gain of about 4 and a half percent in the spine and nearly 2 percent in the hip in patients who were treated with the bisphosphonate immediately.

We also know that more patients in the delayed group actually developed frank osteoporosis compared to those patients in the immediate group. And there were slightly more fractures in patients in the delayed group compared to patients in the immediate group. I think it's important to realize, however, that the overall number of fractures in this study was very small.

They ... found a fairly low risk of recurrence of breast cancer, [but] it was a fairly small trial of only about 1,500 patients, so its ability to [reveal] big differences is fairly limited. But, even given that [limitation], there was a suggestion that patients who had the bisphosphonate added immediately had a lower risk of recurrence of breast cancer. This certainly supports [the idea of] aggressive follow-up of bone mineral density, and this ongoing trial [is] looking at which of several bisphosphonates might be the most helpful, or equally helpful with fewer side effects, when added to initial therapy.

If we shift our thinking to chemotherapy in the adjuvant setting – there are three trials that are, I think, important for everyone to know about. The first of those is a trial that may not have as big an implication for patients [who are being treated] currently, but that will point to a study ... whose results are expected soon. This is a trial known as the FinXX trial. This was another adjuvant trial from Finland that looked at the



incorporation of capecitabine, or Xeloda, into the adjuvant study. It has a fairly complicated study design. In its control arm, patients were treated with three cycles of docetaxel, or Taxotere, followed by three cycles of the combination of cyclophosphamide, epirubicin and 5-FU, or CEF. Patients in the experimental arm had the same three cycles of docetaxel followed by three cycles of cyclophosphamide and epirubicin, but they had capecitabine added to each of those six cycles of therapy – so, initially three cycles of docetaxel or three cycles of docetaxel plus capecitabine; then, in the second phase, three cycles of either CEF – the [C being cyclophosphamide, the E being epirubicin and the F being 5-FU – or CEX, [which includes] capecitabine [instead of] 5-FU.

Lots of things changed in this trial that sort of complicate its assessments. This trial [consisted of] about 1,500 patients. All of them had lymph nodes involved, so they had a higher risk of recurrence. And they were all HER2 negative, since this trial did not include any of the HER2 targeted therapies. Despite that, there was a suggestion that the addition of capecitabine might be better, [as the study found] a slightly lower risk of recurrence in patients treated with the capecitabine-containing regimen. [The study also found] substantially greater toxicity [in those patients treated with capecitabine]; about a third of the patients needed dose reduction, [and there was] a lot more difficulty with mouth sores, diarrhea and the hand-foot syndrome in the capecitabine-treated patients. At this point, [the study has revealed] no difference in overall survival; an additional analysis is expected, and it is certainly important [to conduct an] ongoing analysis of this trial.

The other two trials that are important for us to think about in the adjuvant setting are trials known as NSABP B-30 and BCIRG 005. We'll discuss them [together] because they both evaluated the same chemotherapy regimen. And the regimen is known as TAC: docetaxel, or Taxotere, so that gives you the T; doxorubicin, or Adriamycin, which is the A; and cyclophosphamide, or Cytosan, [which is the C].

Their comparisons were a little bit different. In the NSABP B-30 trial, patients were randomized to one of three chemotherapy strategies: four cycles of Adriamycin and Cytosan, followed by four cycles of Taxotere, with everything given on an every-three-weeks basis; four cycles of Adriamycin and Taxotere – the question being, if you give what we thought were the two most active

agents together, does the Cytosan really add anything to that?; and four cycles of TAC, so all three drugs. [The study was designed to] let us look at, essentially, the same three drugs, but in different combinations and given in different ways.

This trial found that patients who were treated with the sequential strategy – four cycles of Adriamycin and Cytosan followed by four cycles of Taxotere – had a lower risk of recurrence than patients treated with the two drugs or the three drugs given for only four cycles. Now, there were some minor differences in side effects, as well. All three drugs tend[ed] to [result in] increased trouble with mouth sores, slightly more risk of lower blood counts and infections, more issues with fatigue and neuropathy, [but the side effects were more pronounced in] the sequential arm, which incorporated a higher dose of Taxotere. But the bottom line is that there were fewer recurrences in patients who were treated with the sequence of medications.

One of the criticisms, or one of the questions, in [regard to] the NSABP B-30 study was that frequently when the TAC regimen is employed, the TAC is given for six cycles instead of four. And the NSABP B-30 study included only four cycles [of TAC therapy]. They did that because [the purpose of the study was] to look at duration of therapy and to see if the cyclophosphamide added anything. So they had to make some choices in their study design. And, I think especially because the TAC arm did not fare so well in this trial, that question of duration and how that might have influenced the results became a particularly important one.

The BCIRG 005 trial has a [somewhat] simpler design. [One arm of the study incorporated] exactly the same TAC [as that used in the NSABP B-30 study] regimen, but the TAC was given for six cycles of therapy [instead of four cycles of therapy]. [Another arm incorporated] exactly the same sequential four cycles of AC followed by four cycles of Taxotere. So two of the arms from the B-30 study [were the same as BCIRG 005] but [in BCIRG 005 one arm gave] the TAC for six cycles as is commonly done, compared to just the four that the NSABP study had used. [Like the NSABP B-30 trial, the BCIRG 005 trial was] large – it included over 3,100 women – and follow-up has occurred for more than 65 months. [In the two arms of the BCIRG 005 trial.] disease-free survival was [virtually] the same . . . with an estimated five-year disease-free

survival of 78.9 percent in one arm and 78.6 percent in another arm. Also, [there was] no difference in overall survival. They looked at a variety of subsets to see if they could identify patients who might be [better] treated with one option versus another, but they could not find any subsets that seemed to distinguish these two different treatment regimens.

There were definitely more problems with lower blood counts, and with infections when blood counts were low, in patients treated with the concurrent three-drug TAC regimen. Also, [there was] more trouble with low platelet counts, although, overall, that was fairly uncommon. [There was] slightly more trouble with neuropathy and nail changes in the sequential arm – although, when you use all three drugs together, you have to decrease the dose of the Taxotere, [and it's that drug that] accounts for those side effects. So that difference in side effects is perhaps not a big surprise.

So, overall, when I look at these results, I honestly find it hard to justify using the TAC regimen. It's now been compared [to other therapies] in these two large, randomized trials. It's not better than any of the other options. [The result of giving TAC] was either the same or worse, depending on the number of cycles that were given. And the potential for life-threatening side effects was certainly greater.

We also know that most patients who receive the sequential therapy now don't get the sequential therapy on an every-three-weeks basis because you can make [the therapy] truly more effective either by using the taxane weekly or by making the treatment interval every two weeks. So, when we look at these results in aggregate, I personally find it a bit difficult to justify continued use of the TAC regimen.

We will now shift our thinking to those patients who, unfortunately, have metastatic or more advanced disease and focus on new options and information that is important for those patients. First [let's talk about] a trial known as the EGF30008 trial. This trial looked at postmenopausal patients whose tumors were hormone sensitive; they were randomized to treatment with letrozole, one of the aromatase inhibitors, or letrozole in combination with lapatinib. Lapatinib is otherwise known as Tykerb; it is one of the drugs that inhibits the HER2 tyrosine kinase and also the EGFR, or HER1 tyrosine kinase.



This study was specifically done in patients whose tumors were HER2 positive or HER2 negative, with plans to analyze both [subsets] mashed together and then to look separately at patients who were HER2 positive and HER2 negative. They specifically wanted to include HER2 negative patients because, in many animal systems, the emergence of resistance to hormone therapy tends to come about because of increased expression of either the EGFR/HER1 receptor or the HER2 receptor. So there was thought and hope that perhaps, by [combining] these two [medicines], you could prevent or delay resistance to the hormone therapy and allow patients to be treated with hormone therapy for a longer period of time. And certainly, if you do the exact same study in mice with ER positive breast cancers, that's exactly what you see.

This was a study of about 1,300 women. About 225 or so of them had tumors that were HER2 positive. In the group of patients whose tumors were HER2 positive, adding lapatinib made a really substantial difference. So, instead of about 15 percent of patients having their tumors actually shrink by an arbitrary amount, that increased to about 28 percent. And if you looked at patients whose tumors either shrank or remained stable for at least six months or longer, that went from about 29 percent in patients treated with letrozole alone to nearly 50 percent – 48 percent exactly – in patients treated with the combination.

Overall, the average period of time from starting therapy until the disease was clearly worsening and [the patient needed] a new therapy was about three months in those patients with ER positive and HER2 positive disease who were treated with letrozole alone. That increased to just over eight months in patients who were treated with the combination. When they looked at patients whose tumors were HER2 negative, they really couldn't find any improvement in the proportion of patients whose tumors shrank, the average duration of response or the average time it took for patients' diseases to progress and [require] a new therapy.

There are some differences in side effects as well. The most common side effects of lapatinib are diarrhea and a skin rash that looks a bit like acne; like going through puberty again. [Although,] overall, the drug is well tolerated, those certainly were issues for some patients. About 11 percent of patients in the combination-treatment arm needed to stop therapy because of the side effects.

That was the case in only about 3 percent of patients who were treated with lapatinib alone. This is, I think, particularly important, since lapatinib comes in pill form; it does seem to allow those patients whose tumors are both HER2 positive and ER positive to prolong the benefit of all oral therapy that does not include cytotoxic chemotherapy, and, from a quality-of-life standpoint, that may be a very good option for those patients.

There is not a lot of other news on the hormone therapy front for patients with metastatic disease. But there certainly is a lot of very exciting news for patients with HER2 positive metastatic disease; [there are] several new agents that have clear activity in this subset of our patients that [you] need to know about. Perhaps the most exciting of those is a drug that is still in need of a better name. Right now, it's still called TDMI. The T stands for trastuzumab. The DMI is a derivative of maytansinoid. Maytansinoid is a very old chemotherapy agent that, when it was used in its native form, had toxicity that was prohibitive and intolerable, which interrupted its development.

TDMI takes that maytansinoid chemotherapy and binds it to the trastuzumab; it essentially uses the trastuzumab as a way of delivering the chemotherapy specifically to the HER2 positive breast cancer cells. The toxicity is greatly diminished because the chemotherapy is not floating freely, affecting all of the cells in the body. And it should amplify the effects of trastuzumab because you get both the effects of the antibody itself [and] enhanced delivery of the chemotherapy.

We have the results of a phase II study in patients with highly refractory HER2 positive disease. In this trial, all of the patients had previously had trastuzumab. They all had previously had chemotherapy, and virtually all of them had previously been treated with lapatinib. In the patients who'd previously had both lapatinib and trastuzumab therapy, [TDMI] by itself had an objective response rate of about 38 percent. When they limited the analysis to only those patients in the trial whose tumors were really confirmed to be HER2 positive based on central testing, the objective response rate . . . was about 50 percent. About a third of the patients have had a confirmed response – confirmed meaning that images were reviewed by an external radiologist who otherwise has no knowledge of the patients and that at least two sets of scans show that the response has been maintained.

[TDMI] is a very exciting drug that has not had major troubles with toxicity in these early studies and that has a very high response rate in patients [who have previously received] lots of [other] therapies. There are now several ongoing trials that are looking at this agent, both in the very refractory patients with HER2 positive disease and in patients newly diagnosed with HER2 positive metastatic disease.

[TDMI] is certainly not the only other [new] way that one might inhibit the HER2 signaling pathway. We have results of a phase II study of yet another agent – HKI-272, or neratinib. It is similar to lapatinib in that it comes in pill form. It inhibits the tyrosine kinase associated with the internal part of the HER2 receptor. It also inhibits the epidermal growth factor, or HER1 receptor, as does Tykerb. But this one also inhibits the HER3 and HER4 receptors, which lapatinib and Tykerb do not.

This was a trial in two groups of patients, all of whom were HER2-positive. One group had previously had trastuzumab, and one group was newly diagnosed with HER2 positive disease and had not had trastuzumab. In the roughly 66 patients who had previously had trastuzumab, about a quarter of the patients had an objective response. About a third of patients [who previously had trastuzumab] either responded or had stable disease for six months or more. Similarly, in the roughly 66 patients who had not had trastuzumab, objective response rates [were] about 55 percent and about 68 percent either responding or stable for six months or more. This is with the oral tyrosine kinase inhibitor in combination with any chemotherapy.

This drug does have some toxicity issues. Its biggest toxicity problem is diarrhea; in talking to the investigators who've studied this agent, [it appears that,] essentially, everyone treated with this drug gets diarrhea. Many of the patients required Imodium or Lomotil in order to manage their diarrhea. With both investigators and nurses having more experience with this drug and giving better counseling and supportive care to patients, most of the patients [are] able to tolerate this agent and continue its therapy until disease progression – but they certainly often require additional support to manage the diarrhea.

Now, if we think again about options for chemotherapy – we have some additional information from a trial that resulted in the approval of a drug known as ixabepilone within



the last year – actually, it's probably been just over a year, since it's been FDA approved and is available. That trial looked at patients who'd had previous therapy with anthracyclines and taxanes, and it randomized them to either capecitabine or capecitabine with ixabepilone. Overall, that trial showed a significant improvement in progression-free survival, as well as improvement in response rates among the patients who were treated with the combination [of medications]. That's the trial that led to the approval of this agent.

These investigators were able to go back and specifically look at the patients who had triple-negative disease to see if this might be an effective agent in that subset that we now think of as having more aggressive disease. And certainly it was. If anything, the patients who had triple-negative disease seemed to get a bigger improvement in response rate and progression-free survival with the addition of ixabepilone than did [either] the group as a whole or the group of patients who did not have triple-negative disease.

Now, many of you will recall that this combination also has significant toxicity, with trouble with diarrhea, hand-foot syndrome, lower blood counts and neuropathy. And I think that, for many of us, this raises the question as to whether patients in that situation really need the combination or just ixabepilone. We are looking forward to other trials that use this agent to try to figure out how to best use this very active agent and minimize its toxicity to get the best benefit for our patients.

Finally, another question that is important to some patients: if you had doxorubicin or epirubicin, one of the anthracyclines, as initial therapy for your disease and you're now, unfortunately, faced with metastatic disease, is it reasonable ... to think about re-treatment with doxorubicin or another anthracycline? Would there be benefit? Would there be too much toxicity? There is now another formulation of doxorubicin that uses doxorubicin in a liposomal distribution system that really alters how the drug is distributed in the body – it particularly decreases the uptake of the drug by the heart – and that, in some other studies, has limited the potential for cardiac toxicity.

So we had the results at San Antonio of a phase III trial specifically in patients who had received adjuvant anthracycline therapy. [This trial] looked at docetaxel, or Taxotere, alone compared to the combination of docetaxel and the liposomal doxorubicin. Now, like virtually every trial that has

compared two chemotherapy agents to just one chemotherapy agent, patients who got both drugs had slight improvements in [terms of] the number of patients whose tumors shrank or [who] had an objective response, and there was a slight improvement in the time to progression for the overall population, but at the cost of increased toxicity.

Importantly, though, in this study there really was not an increase in cardiac toxicity. So, while this, [to my mind], doesn't really mean that we should use these two drugs in combination, it certainly does confirm that there's benefit from re-treatment with an anthracycline in patients who've had adjuvant anthracycline therapies, and that using the liposomal doxorubicin form is a way to do that that does not bring with it the cost of increased potential for cardiac toxicity.

And I think, Elyse, that I will stop there and open up the rest of our time to questions from your listeners.

ELYSE S. CAPLAN, MA:

Okay. Well, Dr. Miller, as always, you provided a really wonderful overview for women with early stage as well as advanced breast cancer, as well as some of the highlights from the San Antonio symposium this year. Some of it was new information on newer treatments that are available to women today; some was follow-up from trials we've been hearing about over the last number of years; and [some was] longer-term follow-up or enriched or different data. I think it's all really useful.

One of the highlights that I thought was very interesting early on in your conversation was [your discussion] about the aromatase inhibitors' effectiveness [and the fact] that few differences really exist and that most women shouldn't be concerned about which aromatase inhibitor they may take because they all act in a similar way. And I know that, at LBBC, we do get questions from time to time as women switch and change. I think it's great to hear that the research is bearing out that there aren't huge differences among them – and if women can be more comfortable on one versus another, that is really meaningful [in terms of] their quality of life.

I also appreciated – I think our audience probably appreciated – hearing more information on the ZO-FAST trial as it relates to bone health. If we can prevent osteoporosis in a proactive way, I think that's fantastic. And, again, women who

have metastatic breast cancer can feel hope that there are these targeted treatments that are continuing to mature in the research pipeline [and] that will provide more options.

WOMAN:

Doctor, the enzyme test that ... determines the metabolic conversion for tamoxifen – is that currently available from oncologists?

KATHY D. MILLER, MD:

It is a commercially available test. The test specifically looks at the CYP, or CYP2D6, enzyme. It's not a test that we routinely recommend that patients have or incorporate into their treatment decisions at this point, though I suspect, and many of us hope, that that will change when we get more data from the larger studies.

WOMAN:

My question has to do with the length of time a person could be on an aromatase inhibitor – for instance, if you've taken five years of tamoxifen followed by five years of Femara. In my case, I had seven years of tamoxifen and then five of Femara. And I'm being told now to stop taking the aromatase inhibitor. So I'm a little concerned with what the risk is of getting a recurrence at this point, and –

KATHY D. MILLER, MD:

I think the larger context of your question is this: what is the optimal duration of aromatase inhibitor therapy –

WOMAN:

Right.

KATHY D. MILLER, MD:

– or of any hormone-targeted therapy for patients with ER positive disease? Really, at the root of that question is our understanding that ER positive disease has a very long natural history with a very low but long-lasting risk of recurrence on an annual basis. That's what led to the initial studies that looked at an aromatase inhibitor after five years of tamoxifen and what led to that change in practice. It sounds like you've been the beneficiary of those results in having that therapy.

We don't yet have data from any of the studies looking at a duration of longer than five years' treatment with the aromatase inhibitors, whether that's five years up front or after two or three or five or seven years of tamoxifen therapy. There are certainly toxicities of the drug. And the big one that we worry about is bone health. We know that bone loss does slow down when you stop the



aromatase inhibitor. So our current recommendation is to stop therapy with the aromatase inhibitors at five years.

This is very much an ongoing research question, and there are two clinical trials looking at women who are finishing five years of an aromatase inhibitor therapy. [These trials are] quite broad in their eligibility criteria, so they're open to women who are finishing five years of an AI, regardless of whether that was their first therapy or they had been on tamoxifen for some period of time and then switched to an AI. [The trials] will randomize them to either five additional years or no further therapy. [These are] important stud[ies] that will let us see [whether or not there] is additional benefit from longer therapy and [that will help us to] determine the side effects and the cost of that therapy [in order] to allow women to make a more informed decision.

WOMAN:

Okay. Thank you. Just as a follow-up to that – if a person with osteoporosis was getting off . . . I've heard a little about Evista as being a preventative for breast cancer. Is there any type of evidence that Evista, which is good for the bones, would also [prevent a] recurrence [in] someone who's already had [breast cancer]?

KATHY D. MILLER, MD:

Whenever we have looked at the effects of Evista on the breast, [we've found that] they are identical to the effects of tamoxifen on the breast. So, in your mind, you should consider them as being exactly the same thing. They have slight differences in their risk of blood clots and slight differences in their effects on the uterus. We have not been able to identify a single difference. . . on their effects on the breast. So I wouldn't think about Evista in this situation.

I think it's a particularly important point for women who are on an aromatase inhibitor and who are concerned about bone health because, in the ATAC trial, the combination of tamoxifen and an aromatase inhibitor was no better than tamoxifen alone. I worry about women who may be taking an AI, who know they should be concerned about bone health and who are then put on Evista to try to protect their bones – [I worry about] how that might decrease the potential advantages . . . of being on the aromatase inhibitor . . . because the combination of tamoxifen and an AI was no better than tamoxifen alone . . . so I would expect the same thing from an AI and Evista.

WOMAN:

I'm just wondering if there was any information for premenopausal women dealing with metastatic breast cancer.

KATHY D. MILLER, MD:

None of the clinical trials specifically broke out premenopausal versus postmenopausal, so those differences would only come into play in women with ER positive disease, where we were looking at hormone therapies. But that wouldn't affect any of our decisions about chemotherapy options or any of the HER2-targeted agents.

WOMAN:

Okay. If I could just follow up with one thing – I'm being treated with tamoxifen only. And I keep hearing that it's the AIs that cause all the bone and joint pain, and I'm having tremendous bone and joint pain, and I'm starting to get osteoporosis and all that. Is that not also true for tamoxifen, but just to a lesser extent?

KATHY D. MILLER, MD:

It's true for both of them. Whenever they have been compared head-to-head, [it's been found that] those complaints are more frequent or more severe in patients who are on an AI than in those who are on tamoxifen. But that doesn't mean that those are not issues with tamoxifen as well, because they definitely can be.

WOMAN:

I've been on Arimidex for five years, and I was just wondering . . . how do I know how well it's going?

KATHY D. MILLER, MD:

This is really the question that no one likes the answer to. What you're really asking is: how do I know that my adjuvant therapy works and has helped me, regardless of what that adjuvant therapy might have been? The whole goal of treatment in the adjuvant setting is – because we know that some women really do have microscopic metastatic disease that, without adjuvant therapy, will continue to grow and, ultimately, make itself known. And some women have no distant disease at all and really don't need adjuvant therapy.

And we can't tell who's who. Our tests didn't get better just because you got an adjuvant therapy. So, just like I couldn't tell my patients, when we're discussing their risk of recurrence, whether [or not] I would recommend adjuvant therapy [or] if they've really got residual disease, I can't tell them that as they're finishing their therapy, either.

I realize that's a very unsettling thought for women who are getting adjuvant therapy or who are completing their adjuvant therapy. So two pieces of advice for you: Your best judge of how you're doing, really, is how you're doing. And every day that goes by [in which] you have no trouble from your breast cancer makes it slightly less likely that you ever will have a recurrence or trouble from your breast cancer.

In an odd way, your goal is to go to your grave, preferably having died of something quick and painless as a very old lady, without ever knowing the answer to that question, because the only time I can answer that question for certain is when women do have a recurrence of their breast cancer. In regard to all of the healthy old ladies who come back to see me for their 25-year follow-up visits, I don't know if they really needed the adjuvant therapy and it was effective or if they never needed it in the first place.

ELYSE S. CAPLAN, MA:

It's a tough question, definitely, and . . . it's a question we at LBBC hear frequently from women.

WOMAN:

Well, it's a good thing, my doctor tells me – I've also been diagnosed with inflammatory breast cancer [and] chronic leukemia, and every time I go to him, he says, "You can't comprehend your condition." I tell him, . . . "I have a thousand people praying for me," and he says, "Well, it's working."

ELYSE S. CAPLAN, MA:

Well, we appreciate your question and your participation in our programs, and hope . . . for the best, continued good health.

WOMAN:

I was interested in knowing if you had any information about a study that was reported, I think, at the San Antonio conference; that [pertained] to trying to extend the activeness of hormonal therapy by alternating between hormonal therapy and low-dose estrogen.

KATHY D. MILLER, MD:

There actually were two studies that looked at that. They didn't specifically look at alternating. But a very old therapy for women with hormone-sensitive disease was to give them estrogen. In the laboratory, if you take cells that are estrogen receptor positive and grow them in conditions with very low levels of estrogen, for months they don't grow; they look very sickly. They don't die,



LIVING
BEYOND
BREAST
CANCER®

L B B C . O R G

354 West Lancaster Avenue | Suite 224 | Haverford, PA 19041

Phone: (610) 645-4567

Fax: (610) 645-4573

Survivors' Helpline: (888) 753-LBBC (5222)

but they look decidedly unhappy. And, over time, they gradually start to grow again. So they become much less dependent on estrogen.

If you actually look at what happens to those cells, [you'll see that] many of them have become exquisitely sensitive to these very low levels of estrogen. And high levels of estrogen, or levels of estrogen that would be in sort of the normal range for premenopausal women, are now toxic to them because they've become so sensitive to these tiny, tiny concentrations. We used to do this quite commonly with a drug called DES, or diethylstilbestrol. It sort of went by the wayside when tamoxifen was first developed because, in randomized trials, tamoxifen was equally effective but had a lot fewer side effects.

So many of us have still used high-dose estrogen, particularly for patients with ER positive disease that's been very slow growing; for ladies who have been on different hormone therapies with their metastatic disease, sometimes for many years. Since DES is now very tough to get, we have done that using just plain estrogen or estradiol. The dose that is typically used is about 30 milligrams a day. That's a dose that mimics, sort of, the middle to late first trimester of pregnancy, so the side effects are exactly what you would expect: [we] often [see] nausea that can be very much like morning sickness, fluid accumulation, swelling, bloating and an increased risk of blood clots. Those have been the biggest side effects of that therapy.

So, the two studies this year — one was just a series of patients treated, in one particular practice, with high-dose estrogen in that way; it showed that the side effects are pretty similar to those we had seen in those studies with DES from long ago, but that many of those patients had their tumors shrink or remain under control for a much longer period of time. Perhaps more interesting was a small, randomized study that looked at whether [or not] you could use a lower-dose version of high-dose estrogen, if you will — so, instead of 30 milligrams a day, [patients received] six milligrams a day. That was a totally arbitrary selection of dose. The hope was that the lower-dose version might still give the same benefits, but with fewer side effects. And it certainly appeared to be the case. There were no major differences in the responding patients or in patients who were stable for a longer period of time. There still were issues with blood clots, nausea and fluid accumulation, but they seemed to be less frequent and less severe in patients treated with the lower-dose version.

I know of at least one patient in that trial whose disease then progressed on the estrogen; they flipped back to an aromatase inhibitor and her disease responded again. But that was not done in a formal way in that trial.

WOMAN:

[I have] a corollary to a question you received earlier about how long you should take an aromatase inhibitor. I am about to conclude my five years [of Femara, which I began] after [having] five years of tamoxifen ... If they should find, down the road — when I was first given the aromatase inhibitor, [my doctor] said [I'd be on it] for the rest of my life. I wasn't too happy because it's a non-generic. If, however, they decide at a future point — when the end of that study comes through saying, "Oh, those ladies should have been kept on it," will we [be able] to go back on it? Or is [there] kind of a cutoff point? Once I stop, you know, [will I have to] just turn my back on it?

KATHY D. MILLER, MD:

Certainly women like you will have the option to consider whether [or not] resuming therapy would be helpful and a reasonable thing for them to do. I always hope that we have learned from some of our past mistakes. And many women, when they started tamoxifen, were told, "You will be on this for the rest of your life." ... And we later learned that maybe that's not the best strategy and that maybe more than five years of tamoxifen is not really better. I was hoping that, when women started the aromatase inhibitors, we wouldn't make the same mistake ... that kind of set us up for the difficulty of stopping. The reality is that we don't know the optimal duration of the aromatase inhibitors. There are two trials going on right now that are specifically looking at that question. So, for women like you who are finishing their five years of an aromatase inhibitor, the trials to ask your oncologist about are the NSABP B-42 trial ... [and] the JMA-I7R [also known as MA-I7R] trial ... Both of those randomized patients finishing five years of an aromatase inhibitor to either continue with an AI or to continue with a placebo so that we can really answer this question — is longer better? How much better, if at all? And what are the side effects? — so that women really have the information they need to make that decision. Certainly these are drugs that have potential side effects and, as you acknowledge, they cost a lot of money ... So we'd really like to know [whether or not] longer is better in many ways.

[In regard to] your financial situation — in the randomized trials, the drugs are provided. I would expect that, if those randomized trials show a benefit, the women in those trials who were randomized to placebo may be given the option to receive the active drug once we have those results — if it does indeed look like longer is better ... And both [of those trials are] widely available.

WOMAN:

Can you speed up the process of making generic [versions] of non-generic [medications]?

KATHY D. MILLER, MD:

Oh, I wish I were so powerful. [Laughter]

WOMAN:

My question is similar to [that of] the woman who just preceded me, only my total time on tamoxifen and Arimidex was about six years. The question is: could I be encouraging my oncologist to keep me on Arimidex longer?

KATHY D. MILLER, MD:

It's the same answer. We have no data from any study looking at more than five years of an aromatase inhibitor.

WOMAN:

Is that including tamoxifen?

KATHY D. MILLER, MD:

The current recommendation is to stop. But that is an open question. Because some women started with an AI and some may have been on tamoxifen for up to five years or so before starting an AI, the total duration of hormone therapy is often quite different. The two trials that I mentioned allow women who are in all of those situations to enroll. Their only criteria is that you've been on the AI for five years — which, in most cases, they generously define as between four and a half and six years. That gives women the ability to find those trials and get to them.

WOMAN:

What if I don't — what if it was closer to three years?

KATHY D. MILLER, MD:

On tamoxifen or on the aromatase inhibitor?

WOMAN:

No, on the — see, the problem is it's tamoxifen, and let's say that was two years, or two and a half, and then maybe three and a half [years of Arimidex], for a total of six years on tamoxifen and Arimidex.



LIVING BEYOND BREAST CANCER®

L B B C . O R G

KATHY D. MILLER, MD:

So, I think that, at this point, most of us would continue the aromatase inhibitor for five years . . . regardless of how much tamoxifen may have come before you got to that point.

WOMAN:

Okay. So, possibly, I should be encouraging her to return me to the Arimidex?

KATHY D. MILLER, MD:

I think it's certainly a reasonable discussion to have with her.

WOMAN:

I was wondering if there was anything that came up regarding triple-negative disease that is not metastatic. Any developments on what the proper treatment is?

KATHY D. MILLER, MD:

None of the adjuvant trials for which we currently have results were specifically focused on patients with triple-negative disease. Several of them have now looked at that subset, but they have not identified any difference in benefit for the triple-negative subset compared to the results of the trial as a whole. That is changing, though, because with recognition of the uniqueness of the triple-negative subset, there are, internationally, a couple of adjuvant trials currently going on that are targeting triple-negative patients. But at this point, we've not identified a clearly superior adjuvant chemotherapy strategy.

WOMAN:

I am finishing up being on Aromasin for five years. I did take tamoxifen for two years prior to that. My bone density hasn't changed. I am postmenopausal and I'm a seven-year survivor. Do they ever consider – since I had only two years of tamoxifen – going back and doing three more years of that?

KATHY D. MILLER, MD:

At this point we haven't. The only data we have on switching in that order comes from the BIG 1-98 study, [in which] women who had two years of letrozole – so two years of the aromatase inhibitor – and then switched to tamoxifen seemed to do very well; at this point, they seemed to do as well as women who got five years of the aromatase inhibitor. But that's really a bit different than the situation you're describing.

WOMAN:

One other question: You talked about the trials. I'm not scheduled to see my oncologist until July, when I finish up my Aromasin. Are those trials still available at that time? My doctor is from a large medical facility in Ohio. So is it something that you have to be signed up for at this point, or at that time would you still be able to be admitted into that if he thought this was wise?

KATHY D. MILLER, MD:

At this point the trials are still going on and are still enrolling patients. I know that the MA-17R trial has been enrolling very well; it may have completed enrolling patients by July. I don't know how far along the NSABP trial is. They do provide a window so that, if you are anywhere from four and a half to six years on the aromatase inhibitor, you're eligible. If those are trials you're interested in, it would probably be worth a call to your oncologist to see about getting in to see him earlier . . . The only reason the trials wouldn't be available in July is if they've enrolled the total number of women that they need. And they're going well, so it's possible that that will be the case.

WOMAN:

I wonder if there was any progress reported in San Antonio on the development of vaccines to enhance breast cancer patients' immune systems. Could you just speak generally about how that's going?

KATHY D. MILLER, MD:

I didn't see anything new, and there was really very little discussion about vaccines this year. It is certainly still an active area of research. Overall, the earlier trials, I think, were disappointing when we looked at whether [or not] they might prolong disease-free survival in women with metastatic disease who had had an excellent response to their initial therapy. It really seemed not helpful. I know there is a vaccine targeted toward HER2 that has looked very encouraging as far as being able to measure the immune response that the vaccine produces. But those studies really haven't looked at whether [or not] they decrease risk of recurrence or otherwise provide benefit for patients. So, unfortunately, not a lot new from San Antonio this year.

WOMAN:

Can I just ask a follow-up to that? When you think of the patients' breast cancer team, it appears that oncologists obviously are more concerned with the chemotherapy; with the hormone treatments. And when you speak to oncologists about vaccines, there isn't that much interest. So if a breast cancer patient is interested in getting more information about vaccine trials or [things like] that, what medical professionals do you discuss this with to get more help, beyond just going to a government website and looking at the trials that are listed?

KATHY D. MILLER, MD:

I think that actually is the best option. There are still some vaccine trials going on. I think the lack of interest that you're sensing from your local oncologist may be partly [due to his or her] own biases and experience, but it also may be [due to the fact that] the vaccine trials that have been reported thus far really have been disappointing and haven't seemed like they've helped patients.

Some of the national websites that you've been looking at will tell you what trials are available. The centers that I'm familiar with that have done the most work on vaccine trials have been the National Cancer Institute [<http://www.cancer.gov>], the University of Washington, in Seattle [<http://www.washington.edu/>], and the University of North Carolina at Chapel Hill [<http://www.unc.edu>]. It may be worth looking at those individual centers' websites – they may have some local studies that are not yet widely available.

WOMAN:

I was just diagnosed with lobular cancer last week, and I have no other basic information and I have not met with my medical oncologist yet, so this might be a rather funny question. But how – is alcohol; let's say wine – a no-no in breast cancer?

KATHY D. MILLER, MD:

We know that women who regularly drink substantial amounts of alcohol – the equivalent of three drinks a day on a fairly regular basis – are certainly at greater risk of developing breast cancer. There is very conflicting information about whether there is a small increased risk or no increased risk for lesser amounts or less frequent use of alcohol. At this point, no data that I'm aware of suggests that continued moderate use of alcohol after diagnosis alters the



risk of recurrence or behavior of that breast cancer that you now have. I certainly don't advise my patients that they need to stop using alcohol. We do talk about [the idea of] moderation in all things being good for their health. But, beyond that, I certainly don't try to prohibit them from drinking or suggest that their breast cancer will behave differently if they do.

WOMAN:

I was on Arimidex for one month, and my estradiol level went up from the baseline. We switched to Femara for two months, and the estradiol level was still up from baseline, baseline being 19. The two other estradiol levels were in the 20s. My question is: if the estradiol level is still high, are these aromatase inhibitors working?

KATHY D. MILLER, MD:

The short answer is that you should be back on tamoxifen, because what you're describing is that you have functioning ovaries. I'm not quite certain why they were checking your estradiol level after a month on tamoxifen. There are really no recommendations to do so. When we have done this in premenopausal women or in women who still have functioning ovaries, you commonly see the estradiol go up a bit. That doesn't mean the tamoxifen isn't working, because tamoxifen blocks the effects of estrogen on the cells.

WOMAN:

No, I understand that. But I've been postmenopausal for 15 years.

KATHY D. MILLER, MD:

Well, if you're still making estrogen, you are not fully postmenopausal. You may not have had a period, but that is not the same thing.

WOMAN:

Hmm. Well, I'll be 69 next month. And that seems a bit post. But if the estradiol level is still high, maybe the Femara is acting like Clomid and it's pushing the Arimidex –

KATHY D. MILLER, MD:

It can do that. So the larger issue, because figuring out what ovaries are doing is not easy, [is that] tamoxifen in premenopausal women or in women with functioning ovaries can result in their estrogen levels going up a bit, because you block the effects of estrogen on all of the cells in the body, including the cells in the brain that would normally sense estrogen levels. And since they're sensing less of it, they will send signals to the ovaries to make more. The aromatase inhibitors,

which lower estrogen levels, also can result in that same feedback loop, stimulating the ovaries to make more estrogen, because the brain is sensing less of it.

This is one of the reasons we worry about women who are more recently postmenopausal or who [stopped having] periods because of chemotherapy starting immediately on an aromatase inhibitor – because, in some of those women, that will stimulate their ovaries to start functioning again, and not always to the point that they have periods. Sometimes it stimulates them to the point that they have premenopausal estrogen levels and they may not be deriving any benefit from the aromatase inhibitor, but not [to the point] that they're having periods.

WOMAN:

Right. Then should I continue with the aromatase inhibitor or try something different, since the –

KATHY D. MILLER, MD:

For you, dear, it's a complicated question. Without looking at more of the details, I'm a little reluctant to give you individual advice. I think . . . you need to sit down with your oncologist and your gynecologist to figure out what your ovaries are doing and what's the best hormone strategy for you.

WOMAN:

My question [pertains] to DCIS [ductal carcinoma in situ]. I'm almost through with five years of tamoxifen. My doctor had briefly put me on an aromatase inhibitor after about a year, when they thought that there were going to be changes in their recommendations. But it didn't last long. At about that time I also ended up having bone loss; I'm taking a drug to encourage the bone formulation. But I did not have radiation . . . I'm wondering if, when I finish the five years of tamoxifen, I should be planning to take an AI at that point, or if there are still no recommendations on that.

KATHY D. MILLER, MD:

The aromatase inhibitors have not yet been studied, or we don't have the results from a study of the aromatase inhibitors, in patients with DCIS. There are no formal recommendations that would apply to your situation. That said, we have not identified a single therapy that is effective in invasive disease that does not have the same or greater effect in patients with DCIS. I and many of my

colleagues have commonly used the aromatase inhibitors in patients with DCIS – either initially, for women who are postmenopausal, or after some time on tamoxifen. That is outside of their label. We don't yet have the clinical trial data to support this, but I think that many of us are comfortable making that leap.

WOMAN:

This also kind of [pertains] to DCIS. What are the recommendations for persons with positive ER/PR and negative BRCA who cannot tolerate tamoxifen [and for whom] this is the second time through with DCIS and ADH?

KATHY D. MILLER, MD:

There are certainly other hormone therapies besides tamoxifen. For postmenopausal women, it would be very reasonable to consider a trial of the aromatase inhibitors. I have had some luck with switching women who are not able to tolerate tamoxifen to one of the related estrogen-blocking drugs. Two are available on the market. One, which we talked about, is called Evista. But there is another one called toremifene; its trade name is Fareston. They work similarly as far as what they do in the breast. If you look at their side effects – thousands of women have been treated and reported their side effects, [and] they look pretty similar. But many of us have had experience with switching women from one to another, and sometimes we can find one that is simply a better match for you.

ELYSE S. CAPLAN, MA:

And with that, actually, I have to say that our program is coming to a close. I would like to thank Dr. Miller for giving her time, attention, expertise, compassion and sensitivity to all of us today; for really getting us up-to-date; and for helping everyone . . . formulate questions to take back to their health care team that might help them get the information they need to make good decisions about their health care. I also want to thank the women who were able to ask their questions. You always add a dimension to each teleconference program, and even to our ["in person"] programs that we hold here at LBBC, that is unique. We enjoy hearing your voices, your cares and your concerns, and we really want to make a difference in your lives. So thank you for bringing some really important questions.

Clearly, women with hormone receptor-positive breast cancer have a lot of questions as more treatments become available. And the trials



are still ongoing, and it's wonderful and it's frustrating, we would imagine, all at the same time. But we're just going to keep up-to-date and stay in touch with that . . . Dr. Miller, I didn't know if you had one closing comment you'd like to add. I know you're rushing back to take care of your patients.

KATHY D. MILLER, MD:

I thank you all for joining me. My final comment is that we need your help. I sense that many of you are, like us, frustrated at what sometimes seems like the slow pace of progress. The biggest thing that we can do to move progress along more quickly is to complete the ongoing clinical trials as quickly as possible so that we can get these answers. Your participation in a clinical trial when one is available and recommended to you; your help in supporting clinical trials – in urging Congress and insurance companies to actually fund clinical trials – is the biggest thing that you can do to help us make progress for you and your colleagues as quickly as we can.

ELYSE S. CAPLAN, MA:

I think that's a wonderful closing remark. And with that, I thank you, and I thank our participants for their time.

[END OF TRANSCRIPT]