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Early Breast Cancer

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Guests:
Dr. Dan Hayes, Director of the Breast Oncology Program at the University of Michigan Cancer Center
Dr. Lori Pierce, an Associate Professor in the Department of Radiation Oncology, also at the University of Michigan
Gwen Darien, the editor of MAMM Magazine
Advocate Marlene McCarthy from the Rhode Island Breast Cancer Coalition
Advocate Vernal Branch from the Virginia Breast Cancer Foundation

Dr. Susan Love: Thank you for joining us at SusanLoveMD.org for our chat following the 25th Annual San Antonio Breast Cancer Symposium, a conference held last week that brought together clinicians and scientists from around the world to discuss the latest research in breast cancer.

This chat is being sponsored by an unrestricted educational grant from AstraZeneca. Some of you will remember that we've held these chats for the last two years. Last year we focused on quality-of-life issues and this year we decided to look at early breast cancer.

Our guests tonight are Dr. Dan Hayes, Director of the Breast Oncology Program at the University of Michigan Cancer Center, and Dr. Lori Pierce, an Associate Professor in the Department of Radiation Oncology, also at the University of Michigan.

We are also joined by Gwen Darien, the editor of *MAMM* magazine. And our real experts, of course, are our advocates: Marlene McCarthy from the Rhode Island Breast Cancer Coalition and Vernal Branch from the Virginia Breast Cancer Foundation.

A transcript of the chat will be posted on the website within a week and printed in a supplement of *MAMM* this summer.

The meeting was, as always, interesting, and I want to start with Dan and ask you what you think was the most interesting thing about the meeting.

Dr. Dan Hayes: Well, I've been to about 15 of these in a row now, and for a variety of reasons, I came out of this one feeling it was one of the best. One reason why, and this is not an easy answer, is that there was a mixture of reviews and new information that will help clinicians take care of patients today, and a series of really sophisticated talks regarding fundamental, basic science and transnational science that will take care of patients in the future. We had some very nice insights into where we may be going in ways that many of us had not been thinking.

Dr. Susan Love: I would agree with you. What do you think was the most provocative?

Dr. Dan Hayes: Well, for me personally, it's not going to be better ways to treat patients today, which is probably what you want me to say. The most provocative was an afternoon of sessions regarding the interaction between the tissue in the breast that is not what causes cancer, the so-called stromal tissue, the fibrous and supportive tissue, and the breast cancers themselves. We saw a series of four talks (one of whom may be a Nobel prize winner in the future) suggesting that the ductal cells of the breast can't by themselves become cancer, but rather they take the chromosomal damage, the genetic damage, and then are supported by the surrounding stroma in ways that allow them to become cancers.

While this is not entirely novel—for example, we have been thinking about angiogenesis and blood vessel growth that will help a tumor grow—there were some things I hadn't really thought about that will change the kinds of things we do to approach this disease.

Dr. Susan Love: One of the things that came out in that session as well was the effect of radiation on the stroma and how that may affect the normal cells as well as the cancer cells and that the cells may never totally recover from the radiation. It was very intriguing. Dr. Pierce, do you know anything about this work?

Dr. Lori Pierce: There is a lot of work going on to look at factors that may be elicited from those stromal cells. Unfortunately, I was not at the San Antonio meeting. Dan, did they specifically talk about radiation issues?

Dr. Dan Hayes: Yes. Unfortunately, I don't have my paperwork in front of me, but the woman who spoke…

Dr. Susan Love: Mary Helen Barcellos-Hoff from Lawrence Berkeley Laboratory.

Dr. Dan Hayes: Thank you, she took young female animals, removed the breast ductal epithelial bud from them, so all that was left was the stromal tissue in their breast, irradiated that, did not find genetic changes as we think of them in the normal stroma after the radiation, but then found that that stroma would support the growth of cells that are one step away from being cancer, but not yet cancer, that they became cancer when they were put into that irradiated stroma. Whereas if they were put into nonirradiated stroma, they would not grow.

Dr. Lori Pierce: So the factors that were released following radiation supported the growth of precancer cells.

Dr. Dan Hayes: Yes, without that stroma cell becoming cancer itself. I know that Lori's thought about this for a long time, but it raised a lot of interesting issues for me.

Dr. Susan Love: Besides the basic science, which I also find intriguing, there were a lot of clinical studies as well and the presentation that hit the news was the one on dose density. Dan, what is dose density and what exactly did the study show?

Dr. Dan Hayes: This is the one that got the most press; it's the one most likely to affect care now. The concept is that over the last 15 years, there has been a great deal of interest in increased dose intensity, which is taking drug A and giving the same number of cycles of drug A, but giving it at much higher dosage than we normally do. For the most part, studies have turned out not to show that just increasing the dose makes much difference. So in the year 2002 we can say although there is an optimal dose (you don't want to underdose people), that going to high or extraordinarily high doses hasn't panned out, isn't an interesting scientific approach any more, and certainly shouldn't be done on a routine clinical basis.

Having said that, the CSUB about five years ago was, and still is, in the midst of designing trials asking, rather than increasing dose, maybe if we gave the drugs more frequently; so the same dose, but instead of giving it every three weeks, give them every two weeks, or even maybe every one week. This is called dose density. So in this case one might give four cycles of chemotherapy; each cycle used to be three weeks but now you give it every two weeks. So, you only give eight weeks of therapy rather than 12 weeks of therapy, but you give exactly the same amount.

This trial, which was done by the US intergroup mechanism, which is all or most of the cooperative groups together, randomly assigned node-positive women to chemotherapy consisting of Adriamycin or doxorubicin, cyclophosphamide, and paclitaxel or Taxol to either every three weeks or every two weeks. The results showed that with a fairly short follow-up (only 2.5 to 3 years of follow-up) not only were the odds of recurrence outside of the breast lowered by this approach, but so were the odds of dying as well. This was not by a statistically significant amount: only about 2 percent. The group that got it every three weeks had about a 10 percent chance of dying at 2 to 3 years and the group that got it every two weeks had about an 8 percent chance. Now this doesn't sound like much at the surface, but if with time that difference continues to expand, then that would be as important, for example, as adding a taxane to previous regimens that did not have a taxane or, for example, adding Adriamycin to a regimen that didn't have it already. So this may well be a step forward.

I know I am being long-winded, but I will tell you that a lot of oncologists have not had the time to digest this, including some of the leaders in the field. Some feel strongly that we should move to giving therapy every two weeks; others feel that other studies need to confirm this. The upside, in addition to the potential benefit, is that it means therapy is over more quickly and, in fact, it may be less toxic, which is a little enigmatic. It's probably because, to give it every two weeks, we have to use G-CSF [granulocyte-colony stimulating factor], which is Neupogen, and that actually decreases the risk of infection because the white cells come back faster. The downside is that it's more expensive, and it's possible in some of the ongoing trials in which Herceptin [trastuzumab] is being added, that putting the Adriamycin so close together might slightly increase the risk of heart failure. Now, that's not been seen yet, but it's a concern. A lot of oncologists are reviewing these data and trying to decide exactly where to go with them.

Dr. Susan Love: Marlene, do you have any comments about that?

Marlene McCarthy: Coming from an advocate's standpoint is the concern that the insurers are going to be willing to pay for the increased use of Neupogen. We in the advocate community must make sure that the message is clearly understood with medical insurers. Neupogen is supposed to help us not have those white cell counts drop dramatically. So if we're going to have more Neupogen that will cost more money, the insurance must cover us. And they must understand that it truly will be a benefit for the patient.

Dr. Susan Love: I think it is a valid concern. It is also too soon to know what the side effects will be over the long term, as Dan said.

Dr. Dan Hayes: Susan, may I ask Dr. Pierce to provide some comments about this, too? We've talked about this and she has some good insights about the radiation.

Dr. Lori Pierce: From what we discussed from the results from the San Antonio meeting, this will have an interesting and positive impact if we all decide to move to every two weeks with regard to getting the radiation in sooner. One of the concerns is that as we see increasing duration of chemotherapy regimens, that there's an increasing separation between when the surgery was done and when the radiation can be given. While we have some information for the delays of up to 12 or 16 weeks, at more than 12 weeks the delay doesn't seem to have a negative effect on local control. It is a concern that we are getting into regimens where we're seeing Adriamycin/Cytoxan [Cytoxan is a brand of cyclophosphamide] followed by a taxane where the delay is getting longer that we may see problems with local control. So this may be a very positive step to synchronize and sequence the treatments so we can get the radiation in a much shorter time than we currently can with the regimens we are currently using.

Dr. Susan Love: That's an interesting look at it. And now we'll move on to one of our first questions from the audience. Fairygodmother asks, "Was there an update on the Arimidex [anastrozole] and tamoxifen study?" Dan, do you want to talk about that?

Dr. Dan Hayes: Yes, there was. It was an update with one year more follow-up. Frankly, in my opinion not much has changed. Fortunately, for the women in that study, very few patients have died of breast cancer. Many have died of other things, since this is a predominantly older group of women, and the odds of dying of something else in that study remained the same, regardless of which arm they were on.

Perhaps I should review. These were for estrogen receptor- or progesterone receptor-positive patients who had newly diagnosed breast cancer and one-third of them got tamoxifen, one-third got anastrozole, and one-third got a combination of the two. So there was a one-year follow-up. The odds of any first event were decreased in the patients who got anastrozole alone, which was similar to what we saw one year ago. And there really isn't sufficient follow-up or power yet to look at the odds of having a recurrence outside the breast or the odds of survival. What is also presented are the side effects and fundamentally nothing has changed there either. Of note, there continues to be an increased risk of osteoporotic fractures (fractures not related to breast cancer) in the group that got anastrozole alone. I'm not on the American Society of Clinical Oncology (ASCO) panel, but I believe I can speak for them in saying that the conservative approach they announced at the ASCO meeting last year, which is that tamoxifen continues to be the drug of choice in this setting until we have longer and more follow-up of this study and others like it (which will be out in the next year or two), most of us agree that tamoxifen continues to be the drug of choice. The potentially small benefit seen with anastrozole versus tamoxifen may not outweigh the potential complications in the long run. But we don't know that yet.

Dr. Susan Love: Here's a question that was sent in ahead of time. Isabel asks, "Would you be able to tell what the side affects from using tamoxifen versus Arimidex are? I am currently using tamoxifen and I am having a really hard time on it. My doctor is contemplating switching me to Arimidex, but I'm afraid that I will be faced with the same or worse symptoms."

Dr. Dan Hayes: Well, the side effects of Arimidex, in terms of what most patients consider side effects, and these are principally postmenopausal symptoms, seem to be of equal commonality between tamoxifen and anastrozole, because they both arise out of the blockade of estrogen on the part of tamoxifen or decreased production of estrogen on the part of anastrozole.

It is true, sometimes I have patients who can't tolerate one drug, but they can tolerate the other. So in a patient for whom hormone therapy is clearly indicated, rather than going on nothing, in that case that's a perfect role for anastrozole to fill. I'd be interested in what the advocates think.

Dr. Susan Love: I was just going to ask Vernal what she thinks.

Vernal Branch: You know, on the advocacy side, I was sitting in that session and that's the one I found extremely interesting: the ATAC [Arimidex, Tamoxifen, Alone or in Combination] trial looking at the anastrozole and tamoxifen. It showed that the patients on anastrozole did a lot better; they had a lot longer disease-free survival and if a patient is not doing well on tamoxifen, and she clearly needs to be on some type of hormonal therapy, I would suggest she get into a clinical trial. We've always liked evidence-based medicine, and if she fits the criteria, I would suggest she go into a clinical trial to at least try some other type of hormonal therapy.

Dr. Susan Love: It seems to me in my experience that people either do very well or terribly on anastrozole; some people can't take it and other people feel great.

Marlene McCarthy: That's the same with tamoxifen, correct?

Dr. Dan Hayes: More or less. About 30 to 40 percent of women on either drug will have an increase in hot flashes, but I would say the number of women, both from the clinical trials and in my own experience, who just can't tolerate it is less than 5 percent. So a number of women, at least in my practice and most practices, when faced with the substantial survival benefit of tamoxifen and probably anastrozole, compared to hot flashes, are willing to put up with hot flashes, finding them annoying but acceptable. This is not to downgrade what hot flashes can do to a woman's life, but I don't find it's either all or nothing for most women.

Dr. Susan Love: Here's another question from the audience, from Lexie. "What is the recommendation outside of any trials for women finishing five years of tamoxifen? Should they consider taking Arimidex or another drug of that class? In my case I had two bilateral Stage I cancers with negative nodes, no chemotherapy, and five years tamoxifen."

Dr. Dan Hayes: Well, that's a great question. There are at least two and, depending on how you want to review them, three trials asking this question. One of those, done by the US Intergroup, is now closed. It was led by the Canadian part of the Intergroup, the Northamerican Intergroup. It is closed to accrual and we're waiting for follow-up and I imagine it will take at least two or three years, maybe even four more years. One reason why is that the odds of having an event or a recurrence for patients who have reached five years, although not zero, are pretty low. And so the good news is that if you get to five years and your cancer hasn't come back, I can't tell you it won't come back, but I can tell you the odds are much lower than in the preceding five years. And so it's very reasonable to stop tamoxifen in that setting, and most of us feel that is the right thing to do.

I don't believe we have evidence that starting an aromatase inhibitor in that setting is the thing to do until these trials provide evidence that it is, because these drugs are not without known toxicities such as osteopenia and osteoporosis and potentially long-term toxicities. We've only been using the aromatase inhibitors for about 10 years, and the first six or seven years were with people who had metastatic disease, and we just don't have data about long-term treatment and long-term follow-up because most of those patients only take it for a few months or a year. Just like with tamoxifen, it took us 15 years to realize some of the toxicities from tamoxifen that we would not even have begun to have predicted, so that's also possible with these drugs, although I hope it isn't true. I think it is wise to be cautious in that setting given the very real potential that the patient is likely to be cured, which is good news.

Dr. Susan Love: One of the things I worry about is cognitive, or brain, functions and whether there will be problems with that. Marlene, did you see the poster on the effects of hormones on the brain? It seems there really is a "tamoxifen brain."

Marlene McCarthy: Well I was probably in the sixth row deep when that speech was given. I must be honest, I only heard from a distance. But from someone who deals with women all the time from a resource standpoint, we're pleased to see that there's at least some acknowledgment that therapy clearly affects our cognitive function. We know it does. We're just trying to get the scientific community to validate it.

Gwen Darien: Don't you think the scientific community is much more accepting of the cognitive problems that come up with women that we refer to as “chemo-brain”? I think it's become quite accepted.

Marlene McCarthy: I think it depends on what part of the country you're in, actually. If you're close to a research center, a major medical center, or if you're dealing with community oncologists.

Vernal Branch: And there aren't a lot of studies being done on the cognitive part of therapy.

Dr. Dan Hayes: I'm cautious about responding and not sounding defensive, but I think there is an increasing recognition of these problems. Fifteen years ago the efforts were to cure people and to hell with everything else. And I think the last 10 years and especially the last five years, the field has matured to the realization that many, many of the patients we are treating are probably cured in spite of what we do, though we do cure many on top of that. And we have to be very concerned about quality of life. Patricia Ganz from UCLA started a whole field; Charles Loprinzi, who got the Brinker Award Saturday night, started a whole field on the treatment of hot flashes; Rowan Chlebowski, who gave one of the plenary sessions regarding hormone replacement therapy [HRT], has been very carefully studying the effects using PET scanning along with cognitive testing. I agree with all three of you that we could be doing a lot more and worrying more about it and I think we have to take this into account when we recommend chemotherapy, but I believe there is a lot going on that will pay off.

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Marlene McCarthy: I would be interested to know if the cognitive function is not as impaired with the dose-dense model.

Dan Hayes: Yeah, we don't have any idea and that's an area in that trial where there was no effort to test that. One of the reasons is not because we as investigators are lazy, but it's a lot of work and very expensive to do those kinds of studies. I think they'll start being built in more and more and I know the Southwest Oncology Group (because Patti Ganz is in our group) has a real interest in this. So I think there will be more interest, but there's nothing specifically related to that study.

Dr. Susan Love: I actually was speaking to Patti on the plane back from San Antonio. She's doing some very interesting work which I think she'll present at ASCO on PET scanning of women on chemo and then of women plus tamoxifen showing that there really is a specific lesion, a specific area that gets affected.

Dr. Dan Hayes: Yeah, and Ron Chlebowski published in the *JNCI* [Journal of the National Cancer Institute] about six months ago work he's been doing with tamoxifen, so it's interesting. I don't know what we'll do with the information, but it's interesting.

Dr. Susan Love: There were actually several posters that talked about radiation therapy and one of the reasons I wanted to have you on the chat, Lori, was to respond to the movement toward doing intraoperative radiation therapy. In addition, there has been a lot of news lately about MammoSite, just putting a balloon in the breast and radiating locally. What do you think about local radiation alone?

Dr. Lori Pierce: This is a very controversial issue. Although I wasn't at San Antonio, I reviewed some of the abstracts and am aware of the controversies of this very timely issue.

The concept is a very intriguing one. And the concept is whether we can just radiate a part of the breast, and not radiate the whole breast, which has been the standard approach to treating patients following breast-conserving surgery. We know that with the standard approach, the results have been excellent, the local control rates have been very good, and the long-term cosmesis [preservation of bodily beauty] has been good to excellent in most of the patients who have received radiation. We have also noticed in some trials where patients have received lumpectomy only that the majority of the recurrences were at the site of where the tumor was removed. And that has caused some people to suggest that maybe if you irradiate just that part of the breast, that we can have the same outcome as whole breast irradiation. So that's where this idea comes up.

In order to do partial breast radiation, you can do it many ways. You can use a radioactive implant. You can use the MammoSite where you use the balloon as you mentioned. And you use a high dose-rate source to deliver the radiation, and this can be done, we think, over five days, twice a day for five days. You can do this with intraoperative means, as was presented at the San Antonio meeting. You can also do this with external beam where you give just a part of the breast the radiation.

The issue is that we just don't know the long-term data from using partial radiation. Some institutions have done some very important pilot studies that suggested that at five years there are very few recurrences and that patients have done well. But these are in selected institutions and we have no data regarding the efficacy of use of MammoSite.

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Because this is a very controversial and important issue, there was actually a meeting last week just before the San Antonio meeting that I attended at the NCI [National Cancer Institute] in which 35 people were asked to come together to discuss the issues of partial breast irradiation—where things stand in the US and where we are going from this point forward. There is a growing consensus that there needs to be a randomized trial to compare this new concept of partial breast irradiation to whole breast irradiation. And there were members there from the NSABP [National Surgical Adjuvant Breast and Bowel Project] who are putting forth a concept sheet to do this very study to compare partial breast irradiation to whole breast irradiation. I think in the absence of this randomized study, researchers who might be interested in partial radiation, and patients who are interested, can do this within IRB [Institutional Review Board]-approved trials. It is important that patients understand that, while this may be more convenient, we don't know the long-term effects and I think it is best done in a protocol setting.

Dr. Susan Love: I'm glad to hear they are planning to do a big study. I think that is necessary. Marlene, do you want to comment?

Marlene McCarthy: Actually here in Rhode Island, we're aware of only one center that is doing it. There's great interest among newly diagnosed women because it's a better quality of life, not infringing on their time from work and family. But it's not being done within a clinical trial, so we have grave concerns. As the advocate community, we work diligently to build relationships with the medical providers; at the same time, we're trying to make consumers aware that if they're going to participate, while it's exciting to think that you actually may have a better quality of life with a particular treatment, you need to do it within a clinical trial so everyone can benefit. It's always difficult.

Lori Pierce: I hear your concerns; I think you've summarized it perfectly. It sounds like a very positive step in terms of convenience and quality of life, but we just don't want to take a step backwards where perhaps we don't have the same excellent results we've come to achieve with whole breast irradiation.

Marlene McCarthy: It kind of reminds you of sentinel node years ago.

Lori Pierce: There are many parallels. At that meeting, the parallel was brought up many times. At least with sentinel node you do have the confirmatory results of doing axillary dissection to confirm that the sentinel node is negative and your axillary dissection is negative. With this you don't have that immediate feedback so it's even more concerning to me off-study than sentinel node.

Dr. Susan Love: As long as we are on hot (or cold) new things, there were several posters about local ablation of tumors, either radiofrequency or cryosurgery. Lori, do you want to talk about that?

Lori Pierce: I think this is another very interesting set of trials we are seeing the preliminary results from. All of these approaches such as radiofrequency ablation or cryotherapy or even laser therapy try to ablate small cancers, especially without using surgery. Ideally, if we can get very good results from these types of treatment—heating the tumor with radiofrequency ablation or freezing it with cryotherapy—then we may be able to say at some point that we don't need to excise these small lesions when initially diagnosed.

Most of the studies at this point are clearly pilot studies to be able to compare the results with the ablative process—be it radiofrequency or cryosurgery—with the pathologic results when those lesions are excised. We are at an early point in these trials to correlate the ablation with pathologic results.

What's very interesting to me, and I believe it's only been shown for cryotherapy preclinical studies, is evidence that you may be able to actually generate an immune response. You aren't only freezing the tumor and killing the tumor cells, you may also be generating an immune response, so you may be able to confer some sort of systemic benefit from using your local therapy with cryotherapy. And I don't believe that has been shown with radiofrequency ablation. Actually, one of the surgeons in our institution, Mike Sabel, is doing a lot of these studies and has an open study where patients with small tumors are undergoing cryotherapy and then having the lesions excised. And there also are blood studies that are being correlated with regard to immune function in these patients who have the cryotherapy. So it may be a two-for-one. We may not only be getting good local control with cryotherapy, we may also be getting systemic value as well.

Dr. Susan Love: And it brings new meaning to the term "frozen sections." Here's a question from jpm, and it's regarding, I believe, tamoxifen and Arimidex. She asks, "Are these drugs typically used on patients with noninvasive DCIS [ductal carcinoma in situ]? I had that and a mastectomy and am not taking any drugs."

The addition to that would be the interesting paper at San Antonio, Dan, that it was the DCIS that was sensitive to estrogen which was more likely to respond to tamoxifen than DCIS that was estrogen receptor-negative. Do you think we should be doing estrogen receptors on everyone now?

Dr. Dan Hayes: The answer to your question is yes; the answer to the patient's question is that it's more complicated. Fundamentally, in a woman who has had DCIS and a mastectomy, you're no longer treating her cancer because it's all gone with regards to the surgery. So now the only reason for her to take any therapy would be to prevent a new cancer in the other breast. I tell my own patients this is almost as if your sister was just told she had breast cancer and now you have to decide whether or not you would take tamoxifen to lower your risk which has now increased because she has breast cancer, to lower your risk by about 50 percent. This patient's first breast cancer, if it was completely in situ, has now been removed, so she's not treating the original cancer, she is trying to prevent a new one and that is a very complicated question. We have no information about the use of the aromatase inhibitors, in this case anastrozole or Arimidex, for chemoprevention. We will have in the future, but right now we don't and I'd be cautious about using anastrozole in a healthy woman who has a good chance, nearly 100 percent, of being cured of her original cancer.

The second question is, for patients who preserve their breasts, we now have evidence that tamoxifen reduces the chances of recurrence in her breast. Even after radiation it still exists and tamoxifen reduces the risk by about 40 to 50 percent of whatever it was going to be. And Craig Allred presented some data from the NSABP study. The number of tissues he had was far from complete from the participants in the randomized controlled trial, but still very interesting, suggesting as one would expect biologically, the people most likely to benefit from the addition of tamoxifen are those whose tumors were estrogen receptor-positive (ER+) in the first place. We've known that's true about invasive cancer and metastatic breast cancer for years; that the only people who benefit from hormone therapy are those with ER+ or rich tumors. We've not known that about DCIS although we've suspected it, and so I believe Dr. Allred and the NSABP's data confirm my own bias and, in fact, Lori and I at our breast cancer meeting we have at the University of Michigan every week yesterday asked our pathologist to start doing estrogen receptor routinely on all in situ lesions.

Dr. Susan Love: I think the other reason to do it is that the benefit of tamoxifen in somebody with DCIS whose risk is very, very small to start with, is not very big. Anything you can do to maximize that is probably worth it. We've been talking a lot about hormones, and here's a question from our audience.

Dr. Dan Hayes: Actually, Susan, just for a moment to clarify what you said. I agree, but it's not very big because fortunately the patient's odds of getting well are enormous. So it's not that tamoxifen doesn't work, it's not needed in this case. But in those patients for whom there is a need for therapy, we can now perhaps even better select the ones that will most likely benefit.

Dr. Susan Love: Vernal, do you have any two cents to add to this?

Vernal Branch: Actually with the DCIS, a lot of times we don't know which of those cancers is going to go on to be something more serious. And sometimes there's a tendency to overtreat a patient. I would say no to tamoxifen. Why put her on something unless she's estrogen-positive? But that's not something she told us in her question. Was she on tamoxifen already?

Dr. Susan Love: No, she wasn't.

Vernal Branch: I would say no.

Dr. Susan Love: It is true, too, that the studies were on women who still had their breast, who had breast conservation. She had a mastectomy.

Vernal Branch: The only reason to have tamoxifen is to save her other breast, but we don't know her hormone status.

Dr. Susan Love: Here's a question that will shift us a little, and I can hear people complaining already that we've spent too much time on hormones. "What adjuvant therapies are now being targeted towards ER-negative, lobular cancers?" (Actually most lobulars are ER-positive.) "Do we have any new research data?" Dan, why don't you speak mostly to ER-negative.

Dr. Dan Hayes: We don't have any chemotherapy that is necessarily specific for ER positive (ER+) or ER negative (ER-). In fact, if anything, chemotherapy in general seems more likely to work in ER- patients. Second question, what are those ongoing studies? Well, the one that was the most exciting, of course, I've already discussed from San Antonio, and that was the dose-dense trial. There are four large ongoing trials being done in the world for patients whose HER2 is positive, asking whether or not adding Herceptin to chemotherapy or after chemotherapy provides benefit [HER2 is also sometimes referred to as HER-2 or Her-2/neu or erb-b2]. And these trials are ongoing and will have

5,000 to 6,000 women and we should have an answer to that hopefully in the next four to five years, and perhaps sooner.

Other studies that are closed but we are waiting to hear the results from: one is a comparison of paclitaxel versus docetaxel and those brand names are Taxol versus Taxotere; that trial is closed. That trial also asks another dose-dense question: It asks whether or not those drugs are better given once a week or once every three weeks. There's another trial out of Canada, asking a fairly dose-dense question versus standard AC [doxorubicin, cyclophosphamide] followed by Taxol, which is ongoing now, and is open in most of the centers. And then there are some new trials just opening up. One is asking in good prognostic women whether or not you need combination therapy, so it's actually looking at combination Adriamycin [doxorubicin] and cyclophosphamide versus single-agent Taxol alone. And there's another one for elderly women that's going to look at CMF [cyclophosphamide, methotrexate, and 5-fluorouracil] or AC, whichever the physician chooses, versus single-agent Xeloda [capecitabine]. One way we are going here is seeing whether a single very effective agent is just as effective and less toxic than combination therapy.

Gwen Darien: The other trial I heard people talking about was the addition of platinum to Herceptin.

Dr. Dan Hayes: Yes, the translational science in this regard is that when Denis Slamon and Mark Pegram and Mark Petras's lab first started looking at the antibody that is the basis for Herceptin, they started looking at it in combination with chemotherapy as well as by itself and found that, of the chemotherapies they tested, one of the ones in which it seemed the most likely to create synergism (which means one plus one makes more than two) was cisplatin or carboplatin, either one. They ran a Phase II [trial] that I was privileged to be part of with cisplatin and we saw patients with metastatic disease have nice responses with Herceptin plus carboplatin which we hadn't expected to see. So now there was a randomized trial for patients with metastatic disease looking at adding carboplatinum to a taxane and Herceptin versus Herceptin and taxane alone and there appears to be an increased response rate. I believe that was a favorable study, but whether that should be routine in the metastatic setting, I don't think it should be because the toxicities are greater. But nonetheless, it does suggest we have another option of adding a platinum-based agent to Herceptin in patients with metastatic disease.

There is a similar adjuvant trial now being run by the Breast Cancer International Research Group (BCIRG). It is one of the four trials I just described in which Herceptin is being studied; but one of the arms there has no Adriamycin at all. It is a taxane plus carboplatin plus Herceptin, so a very interesting and innovative approach, I think.

Dr. Susan Love: Here's a question that sort of relates a little to this that we received earlier. "My mother had polio in the early '50s and was left with a very weak immune system. She is now recovering from recent radical breast surgery due to cancer, and is worried about the effects of the chemotherapy on her already weakened immune system. She is 83. Should she have the chemo or not?"

Dr. Dan Hayes: Well, I guess that's me again.

Dr. Susan Love: And I bet the advocates will have something to say too.

Dr. Dan Hayes: There are a number of questions, which is whether chemotherapy for anyone in their 80s is worth it. That's always a judgment call; we have no clinical trial data for women in that age. I'm very conservative with women that age. First of all, most of those women are ER+, and I would be in favor of treating her with hormone therapy if that was appropriate.

Second of all, chemotherapy is of decreasing benefit in older women—we don't know why, but it's been shown over and over again. Not that it has no benefit, but it is decreasing. And third of all, it has increased toxicities, so I'd be reluctant to recommend chemotherapy to this patient unless she was in superb shape and had an expected survival of many years.

Let me add another thing and that is the concern about these drugs on the immune system. First of all, chemotherapy clearly damages the immune system for short periods of time, in terms of weeks. What we haven't seen in people who go through chemotherapy and then recover are long-term immunodeficiencies. So we have not seen the kinds of syndromes we expect with long-term immunodeficiency like, for example, what we've seen with AIDS and organ transplants where the immune system is chronically depressed, so that's good news.

Dr. Susan Love: Let me just throw in Lexie's section since it relates to this. She may have rheumatoid arthritis and says, "If I do have rheumatoid arthritis the drugs they use to treat it are cancer drugs and I am scared they will lower my resistance and cause a recurrence of my cancer. Your thoughts on the subject. Have you had any experience with other survivors who have rheumatoid arthritis?"

Dr. Dan Hayes: Yes, that's where I was going, a lot of people are worried that a reduction in their immune system will relate to their cancer returning. In fact, I don't think I speak alone, most of us don't believe that the immune system has anything to do with the suppression of solid tumors like breast cancer and colon cancer. The immune system has really evolved to keep us from dying of pneumonia or tuberculosis—infectious diseases. We've evolved many, many other systems to keep us from getting cancers early, and they don't appear to involve the immune system, which is probably good news, and that's why most of us don't have lupus or rheumatoid arthritis because we wouldn't want the immune system going after our own cells, and cancer cells are very similar to our own cells. Therefore, there's no evidence that people who have gotten chemotherapy have an increased risk of either recurrence of their cancer or an increased risk of other cancers coming out other than those few cancers we know the chemotherapy itself causes by damage of the genetics. So we know, for example, that some therapies cause leukemia, and we don't use them any more or, if we do, we use them very carefully. So I counsel my patients that the benefits of the chemotherapy in terms of preventing recurrence or of palliating them in the metastatic setting are real, and there's no real evidence that damaging the immune system in the short run—in terms of dropping white blood cells and that sort of thing—-in any way results in cancers coming back. Likewise, people who have autoimmune diseases and require low doses of chemotherapy like cyclophosphamide or Imuran [azathioprine] don't appear to have an increased risk of either new breast cancers or, if they are treated for breast cancer, an increased risk of recurrence. So, I believe that woman should be treated just like any other women.

Dr. Susan Love: I have another question we just got. Maybe Lori will speak to this. "I recently read in *AARP Bulletin* that an Italian study indicated the same survival rate for women with lumpectomy, lumpectomy with radiation, and mastectomy. Do you know of this study, and can you comment?"

I sure hope you know of that study since it is the basis of your whole work, but do you want to comment on what was really reported?

Lori Pierce: On the long-term study from Milan?

Dr. Susan Love: Right, and we also have the long-term NSABP.

Lori Pierce: Just recently there were two papers, studies that we have known for a long time, that were both updated. One was from Milan and one was from the NSABP. We'll talk about the NSABP since that's the American study; it compared lumpectomy or lumpectomy plus radiation versus mastectomy. And what these studies show, as they've shown before but now with 20 years of follow-up, is the survivals are the same. Patients do not have to have a mastectomy; patients with early stage breast cancer who have a single cancer where the tumor can be excised and margins are negative and who then go on to radiation, those patients do equally well in terms of survival as if you have a mastectomy.

That study also shows, because it had an arm where patients just got a lumpectomy, unlike the Milan trial, so that we can compare lumpectomy versus lumpectomy and radiation. There was a significantly higher recurrence rate in the breast of those who did not have radiation and there was also a difference that was almost significant with regard to disease-free survival in favor of those who had radiation versus those who did not. So it supports the standard of care in this country for patients who want breast-conserving therapy that they have radiation, to the whole breast by the way, following lumpectomy.

Dr. Susan Love: There were two interesting other reports in San Antonio which go along with this that you might want to comment on. One was that older women who did not have radiation therapy had a higher rate of recurrence. There's been some tendency to think that if you're in your 70s or 80s you can get away without radiation. And the second study was out of the ATAC trial we mentioned earlier that women in other countries are more likely to get breast conservation and women in this country actually have a higher rate of mastectomy.

Lori Pierce: It still amazes me how there is such a big difference between other countries and our own country. Even though we have been such proponents and have run large trials showing the equivalence in terms of survival of breast-conserving therapy with radiation versus mastectomy, how so many women in this country still have a mastectomy. It's unclear to me whether all women at this point in time are presented with the option of breast-conserving therapy. Because the vast majority of women with early stage breast cancer are excellent candidates for a lumpectomy and radiation, in that they do just have a single tumor. They are patients who, if you look at the studies, will clearly have the same outcome if they had breast-conserving therapy or a mastectomy. So it just shows that there is still more work to be done.

Dr. Susan Love: Vernal, do you want to comment?

Vernal Branch: The information keeps changing. I think women need to know, need to be given the facts. And when you give them the facts, it's a personal decision. A lot of women are just so afraid of breast cancer. They're probably not given all the facts. They're still not processing it at the time they're given the diagnosis. Hearing these figures, I don't know the difference between European and American women regarding preserving the breast, but I find it really alarming.

Dr. Susan Love: I think what sometimes happens is that, in the heat of battle, when a woman is newly diagnosed, she says maybe I should just have my breast off and not worry about it; and the surgeon says okay, instead of going over the options. And in addition, she says maybe I should have the other one off too, and he says fine.

Vernal Branch: I think they're so afraid they're going to get breast cancer back. I'll just take the breast off and be done with it and then not have to worry about it.

Dr. Dan Hayes: Susan, you didn't hear me. I said, or SHE says fine.

Dr. Susan Love: You're right. Here's another question from the audience which shows you again how this may not always be perfect. "I had DCIS, very extensive, had a mastectomy, I took no drugs...less than a year later I had a recurrence. Was this most likely the DCIS that got out of the bag?" Go ahead, Lori.

Dr. Lori Pierce: Actually now we're on DCIS, but I wanted to bring up the point with regard to invasive breast cancer. Many women still think, because these notions aren't addressed in the initial meeting with the physician, that when you have a mastectomy you will never have a recurrence in the tissue that remains, and that's probably one of the key points that must be conveyed to patients—that even with mastectomy, there is still a chance of recurrence.

Dr. Susan Love: Absolutely.

Gwen Darien: There's the sense that if you have the surgery, you get it all out.

Dr. Susan Love: I wish.

Gwen Darien: You hear women saying that all the time, even if they're sophisticated.

Dr. Susan Love: As a surgeon, mastectomy is just a very wide excision. It's not like the breast has these nice boundaries and you know that you've gotten it out.

Dr. Dan Hayes: To jump in I've actually seen two patients this week who had breast conservation some time ago and both have had recurrences in their breast, and both of them said they wished they'd had mastectomies. And the reason I'm bringing this up is that women who are listening on this line or who will be on the website should understand that their choice to have breast conservation, and this echoes Lori's previous comments, was a good one.

What I'm afraid of is that someone's friend has an in-breast recurrence and then she'll decide to have a mastectomy because "look what she did" and that was wrong. What we know from the large trials (and besides the two you reported, there are others on thousands of women) is that your odds of surviving in the long run are just as good with breast preservation as with a mastectomy. And if you have breast conservation and you do have a recurrence in that breast, many patients still do quite well in the long run. So one shouldn't be swayed by what one's neighbor had, and make the wrong decision in the heat of the battle, as you were saying earlier.

Dr. Susan Love: Right. And there's also a tendency to have magical thinking, that if I offer my breast up to the gods, I'll get my life in exchange. And I wish it worked like that, but it just doesn't.

I have one last question, and it's a big one, that I'd like you to address, Dan, before we close. "What role does blood work have in monitoring recurrence? My tissue is treated, but what do I do with all the anxiety and feelings? I am really seriously considering walking away from all the appointments and follow-up! If the tests mean nothing—why put myself through all the invasions and anxiety? Besides if my cancer returns, there is no save, only more treatments!"

Dr. Dan Hayes: Well, I wouldn't be as fatalistic as this woman, but I kind of agree with her and so do most of the governing, expert guidelines panels. ASCO has had two separate ones and there are a couple in Europe who are suggesting that routine blood testing and routine bone scanning and whatever else you want to do in asymptomatic women with no evidence of recurrence is more than a waste of time and money, it might do harm because the false positive rates are high in these patients. I don't do any of it. I see my patients personally, routinely mostly, to make sure they've had the opportunity to ask questions and have them answered, to have physical examinations. I do routine mammography on them because their risk of a new cancer, not a recurrence but a new cancer which can be cured, is higher than the average woman. So, there is a reason for follow-up but not a reason for the routine tumor markers and routine bone scans and CT scans. I actually have a conflict of interest for tumor markers; I should be encouraging people to do this since I have something to do with them, but this is a setting where it's just not appropriate.

Dr. Susan Love: Very good. We just got one last question, so I want to get it in, and then we'll call this to a close. Sharon asks, "I had a lumpectomy. My lymph nodes were negative, but my pathology slides showed vascular invasion. I was told by one oncologist that vascular invasion is just as significant as a positive lymph node. Do you agree?"

Dr. Dan Hayes: Not quite. But, first of all, lymph invasion is not as reproducible from one pathologist to another as is the presence or absence of lymph nodes. Second, when a pathologist is reading all the slides and then publishes his or her own data, it's never quite as powerful as having a true positive node. On the other hand, with a patient who is on the fence with regard to other factors, maybe she has negative nodes, maybe a 2cm tumor that's moderately well-differentiated, and she isn't quite sure what to do, the presence of documented lymphatic invasion might push her toward getting chemotherapy when she wasn't thinking of it otherwise. But for an individual patient, that's a very personal question that needs to be addressed by the oncologist who has reviewed all the data for that patient.

Dr. Susan Love: This is the REALLY last question. This one is for Lori. People are getting up their nerve now as we need to close down. "I had radiation 24 weeks following my lumpectomy (2.2cm tumor, 3 positive nodes); chemo was CAF [cyclophosphamide, doxorubicin, and 5-fluorouracil], 6 cycles. Should I be concerned about the delay?"

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Dr. Lori Pierce: Certainly most of the studies that have been done have given radiation within a month or so following completing of chemotherapy. In this case, she received it 24 weeks after her lumpectomy. (And she doesn't say how long after the chemotherapy.) In general, it is a tough question and as I mentioned earlier, as we see longer delays, there are concerns that perhaps a delay might affect the risk of local recurrence, but there is no data saying that is the case.

Dr. Susan Love: Nor is there data saying it would affect survival, correct?

Dr. Lori Pierce: Absolutely, it is a local control issue.

Dr. Susan Love: So in the worst case, she might get a recurrence of cancer in her breast, but there's no evidence to show it affects whether she lives or dies.

Dr. Lori Pierce: That is correct. So while the controversy may be there for local control, there isn't even good data for that, and certainly no data with regard to survival.

Dr. Susan Love: If we didn't get to your question, please submit it to Personal Guidance on the website.

I want to thank everybody so much for joining us tonight. I especially want to thank our participants: Drs. Dan Hayes from the Breast Oncology Program and Lori Pierce from Radiation Oncology at the University of Michigan; Marlene McCarthy from Rhode Island Breast Cancer Coalition; and Vernal Branch from the Virginia Breast Cancer Foundation. And thanks to Gwen Darien, the editor of *MAMM* magazine, which will be distributing a transcript of the chat as a *MAMM* supplement this spring.

Thank you all very much; and thank you to our sponsor, AstraZeneca. Have a very, very good evening and happy holidays.