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Meet The Professors

A case-based discussion on the management of estrogen receptor-positive breast cancer in the adjuvant and metastatic settings

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Meet the Professors: A case-based discussion on the management of estrogen receptor-positive breast cancer in the adjuvant and metastatic settings

STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well-informed of these advances. In order to incorporate research advances into developing treatment strategies for patients, the CME program *Meet the Professors* utilizes case-based discussions between community oncologists and research leaders.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Develop and explain a management strategy for treatment of ER-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of aromatase inhibitors in the adjuvant setting and of sequencing aromatase inhibitors after tamoxifen.
- Describe a strategy for sequencing hormonal therapies in the metastatic setting for patients with ER-positive metastatic disease.
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the treatment of noninvasive (DCIS) and invasive breast cancer.

EDUCATIONAL METHOD

To receive CME credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form.

ACCREDITATION STATEMENT

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CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 4 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

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Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
conjugated estrogens	Premarin®	Wyeth Pharmaceuticals
cyclophosphamide	Cytoxan®	Bristol-Myers Squibb Company
	Neosar®	Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Adriamycin®	Pfizer Inc
	Rubex®	Bristol-Myers Squibb Company
exemestane	Aromasin®	Pfizer Inc
fluorouracil (5-FU)	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
goserelin acetate	Zoladex®	AstraZeneca Pharmaceuticals LP
letrozole	Femara®	Novartis Pharmaceuticals
leuprolide acetate implant	ViadurTM	ALZA Corporation
	Lupron Depot®	TAP Pharmaceuticals Inc
methotrexate	Various	Various
paclitaxel	Taxol®	Bristol-Myers Squibb Company
raloxifene hydrochloride	Evista®	Eli Lilly and Company
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
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Editor's Note

Miami symphony

This is the third time we have gathered four clinical research leaders and about a dozen community-based medical oncologists to produce a *Meet the Professors* audio program. Along the way we have learned a great deal by experimenting with this dynamic case-based approach to production. Last year in Dallas, the room had a bit too much echo, while our November meeting in New York suffered from mild claustrophobia. However, for our most recent event this spring in Miami, we pretty much got it right.

Even more important than "concert hall" acoustics is the cast of musicians and the orchestral score. These events are not rehearsed but rather improvised, and as the "conductor" it is my responsibility to select symphony members who are not only talented but also quick-thinking. Our latest ensemble instantly meshed, and the result was a lively and informative day of discussion. In fact, it was extremely challenging to edit this program because there were so many valuable and interesting comments.

Prior to these *Meet the Professors* sessions, I routinely confer by telephone with each community-based participant to select interesting cases to spring on our research leader faculty. The research leaders walk into these meetings with no prior knowledge of the cases that will be presented. The first case you will hear in this program exemplifies the most common adjuvant clinical scenario — a postmenopausal woman with a node-negative, ER-positive tumor. When Tom Cartwright told me about this 62-year-old woman, I immediately appreciated how astute he was in suggesting this case. What makes this presentation even more interesting is that some years ago, Tom had also provided care for this patient's mother, who was treated with tamoxifen.

Tom selected this case to illustrate the changes in breast cancer management that have occurred from the prior generation to this one. His patient decided to be treated with adjuvant anastrozole and forego chemotherapy, partly because of the result of the Onco*type* DX™ assay. The initial data from this fascinating new Genomic Health assay was reported by the NSABP's Soon Paik only months before at the last San Antonio Breast Cancer meeting.

From my perspective, the issues discussed in this case reflect some of the most important recent changes in breast cancer therapy since the patient's mother was diagnosed in the 1980s. On one hand we see a potential shift towards less chemotherapy and more effective hormonal therapy, and simultaneously, a shift toward focus on absolute versus relative risk reduction estimates in discussions with patients. These are highly tangible benefits now reaching patients, and each of our faculty — Peter Ravdin, Gershon Locker, Kevin Fox, and Richard Elledge — have had a role in the evolution of this change in research and practice.

The other cases selected for discussion were equally pertinent and reflect the infinite number of challenges every medical oncologist faces when treating women with this disease. You will hear these physicians discuss such challenging issues as the role of adjuvant LHRH agonists, the use of tumor markers in management of metastatic disease, compliance with oral endocrine agents (and a patient who "doesn't like doctors"), the choice of systemic agents in patients with rapidly progressive ascites and breast reconstruction in patients with metastases. It was a privilege to be the conductor of this stellar ensemble. The artists were creative, thoughtful and truly put on a great performance. I hope you enjoy their rendition and work.

—Neil Love, MD
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CASE 1: A 62-year-old woman with ER/PR-positive, HER2-negative multicentric breast cancer (from the practice of Thomas Cartwright, MD)

- Routine annual mammogram revealed changes from the previous year
- Ultrasound revealed three suspicious lumps in the right breast
- Biopsy was positive for infiltrating ductal carcinoma
- Underwent a lumpectomy for two 1.5-centimeter tumors and one 1.0-centimeter tumor
- Tumors were Grade III, ER/PR-positive, HER2-negative
- Sentinel lymph node was negative
- Prior hysterectomy and a history of osteoarthritis, hyperlipidemia and hypertension

Key discussion points:

1. Evaluating prognosis for multicentric breast cancer
2. Use of chemotherapy in patients with ER/PR-positive, node-negative breast cancer
3. Selection of adjuvant hormonal therapy in postmenopausal women
4. Use of the Onco*type* DX™ breast cancer assay to assist in making decisions about adjuvant chemotherapy

DR CARTWRIGHT: This 62-year-old woman underwent a routine annual mammogram which showed a change from the previous year. An ultrasound revealed three suspicious lumps in a cluster in the right breast, and a biopsy was positive. She underwent a lumpectomy and all three lesions were removed. The tumors were Grade III infiltrating ductal adenocarcinoma. Two of these measured 1.5 centimeters and the third was one centimeter. They were all ER/PR-positive and HER2-negative. The sentinel lymph node was negative.

The patient was otherwise in good health. She had undergone a hysterectomy in the past and was on hormone replacement for many years. She had a history of osteoarthritis, hyperlipidemia and hypertension. Interestingly, her mother was a patient of mine who took tamoxifen for five years in the 1980s.

DR LOVE: Peter, what do we do when we have three different primary tumors removed? In a prognostic index, does that count as a 1.5-centimeter tumor or a 3.5-centimeter tumor? Also, can you describe what you think her risk would be?

DR RAVDIN: In terms of a patient who has multiple primary tumors, there isn't an absolute answer. To some degree, the right thing to do is to think of each one as an independent tumor that confers additively to the risk. The first tumor gives her a risk of mortality at 10 years of about 10 percent,

being a T1c. In addition, she has another T1c tumor and a T1b tumor. Putting all of that together, she probably has a 20 to 30 percent risk of mortality at 10 years, which is certainly equivalent to having a T2 tumor — this is not a low-risk breast cancer.

DR LOVE: One of the things we want to get into is the question of which hormonal therapy to recommend for this woman. Gershon is one of the main investigators on the ATAC trial. One of the more interesting recent outcomes of that trial was the 2003 San Antonio presentation by Mitch Dowsett evaluating outcome based on progesterone receptor results. This woman has an ER-positive/PR-positive tumor. Is that relevant in this case?

DR LOCKER: That ATAC presentation was a retrospective subset analysis, and that's a very important consideration. Most of the data presented from ATAC were prospective evaluations. In that retrospective analysis, the women who were ER-positive and PR-positive had an advantage when they received anastrozole compared to tamoxifen. However, in the subset of women who were ER-positive and PR-negative, the benefit was markedly greater for women who were given anastrozole. The hazard ratio was about 0.5 compared to tamoxifen. It's very interesting, but I'm not willing to make decisions based on that data alone.

With regard to this patient, I think the decision to use anastrozole or tamoxifen shouldn't be based on the hormone receptor analysis. This is a woman who is ER/PR-positive, and the data support the superiority of anastrozole over tamoxifen.

DR LOVE: I interviewed Mitch Dowsett in San Antonio after he gave that presentation, and he was speculating that perhaps this subset of patients might be the HER2-positive patients. He seemed to think there was a correlation.

DR LOCKER: There is some suggestion that women who are HER2-positive and ER-positive have lower levels of ER and are more likely to be PR-negative. There is data, particularly from neoadjuvant studies of anastrozole and letrozole, to suggest that anastrozole and letrozole are superior to tamoxifen in that subset of women whose tumors were ER-positive and HER2-positive.

A potential explanation is that in the presence of HER2 overexpression, the coregulators present when tamoxifen binds to the estrogen receptor may actually be those that make tamoxifen seem more estrogenic than antiestrogenic. This is not an issue for women receiving anastrozole because anastrozole doesn't bind to the estrogen receptor and there's little, if any, estrogen to bind to the receptor. If that's the theory, it would be reasonable to assume that in patients with HER2-positive tumors,

Results of Analysis of Time to Recurrence in the ATAC Trial According to Estrogen and Progesterone Receptor Status

Receptor status	n	Anastrozole vs tamoxifen*
ER-positive, PgR-positive	5,704	0.82 (0.65-1.03)
ER-positive, PgR-negative	1,370	0.48 (0.33-0.71)
ER-negative, PgR-positive	220	0.79 (0.40-1.5)
ER-negative, PgR-negative	699	1.04 (0.73-1.47)

*Hazard ratios less than one indicate values in favor of anastrozole

SOURCE: Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (arimidex, tamoxifen, alone or in combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;**Abstract 4.**

anastrozole and other aromatase inhibitors might be superior.

DR LOVE: Tom, I know you utilize Peter's ADJUVANT! program (http://www.adjuvantonline.com) and you actually entered this woman's data into the program. Can you tell us what you found?

DR CARTWRIGHT: I did plug her numbers into the ADJUVANT! program, and the chemotherapy regimen I plugged in was for doxorubicin/cyclophosphamide. Eleven out of 100 women benefit from hormonal therapy, and one out of 100 benefit from adding chemotherapy.

DR LOVE: Peter, what are your thoughts on this, and does your model also provide response rates based on tamoxifen versus anastrozole?

DR RAVDIN: The last overview analysis showed that in postmenopausal women — particularly if they were ER-positive — a conventional chemotherapy actually conferred relatively little advantage. In fact, it was slightly less than a 10 percent proportional risk reduction, which is far less than can be expected from hormonal therapy. Hormonal therapy is quite important to these women.

The ADJUVANT! program provides firm values for 10 years based on tamoxifen but, of course, we don't have that kind of data for the aromatase inhibitors. If you select an aromatase inhibitor, ADJUVANT! will provide an estimate, based on certain assumptions, from the first four years of the ATAC data, but it has to be clearly stated that we're still looking for long-term efficacy and safety data for the new aromatase inhibitors.

DR LOVE: Before we go on with this case, I'd like to ask Gershon, in general, what's your approach to the postmenopausal woman with ER-positive, node-negative tumors?

DR LOCKER: I agree with Peter that the story with the aromatase inhibitors is still in progress, but we have hard data from the ATAC trial and we will certainly have even more data this summer after another analysis of the data. Virtually all of the patients will have completed therapy for that analysis.

However, so far the absolute difference between tamoxifen and anastrozole, based on four-year data in women such as the one that was presented, is about one to two percent. If you use Peter's ADJUVANT! program, that's the same one to two percent that comes from adding chemotherapy to tamoxifen. So, I tell patients the story for chemotherapy is not clear-cut, and it's not clear-cut in this patient for whom the benefit is only a few percentage points. Anastrozole may actually accomplish the same thing as tamoxifen plus four cycles of AC.

I explain that this is preliminary data based on a median of four years follow-up and making assumptions that nothing else will change. I think it's a reasonable discussion to have with patients, explaining the differential in terms of the benefit from chemotherapy.

DR LOVE: Overall, what fraction of women like this patient receives chemotherapy?

DR LOCKER: In my practice, approximately half of the patients with node-negative disease who do not have any other high-risk factors receive chemotherapy. I do not pressure them to take chemotherapy. I give them a choice and explain the data. Peter's ADJUVANT! program has made it much easier for us because we can provide them with "hard" numbers.

DR LOVE: It's interesting that when we asked more than 700 breast cancer survivors in our patients' perspectives project last year, "If you were in this situation again, would you want to receive AC or CMF chemotherapy for a one percent improvement?" about 55 percent of them said, "Yes," which seems to correlate with Gershon's experience in practice.

I want to ask Tom about the next step he discussed with this woman, because there's an interesting twist in this patient's situation.

DR CARTWRIGHT: I actually went one step further and ordered the Onco*type* DX™ breast cancer assay, which was just approved by the FDA. It's made by Genomic Health and is based on the information

presented at the 2003 San Antonio Breast Cancer Symposium. It costs about $3,400 and it took several weeks to get the insurance company to agree to pay for it.

The assay is based on women with Stage I or II, node-negative, ER-positive breast cancer who are treated with tamoxifen. The risk goes from one percent up to almost 50 percent. This patient's recurrence score was 21, which means her risk of relapse at 10 years is approximately 12 or 13 percent. This is almost exactly what was predicted from the ADJUVANT! program.

DR LOVE: The presentation by Dr Paik in San Antonio was one of the most interesting at the last meeting, and everybody came away thinking, "Is this really ready for prime time? Is it worth the money? What does it really mean?" Peter, could you review what the study showed and whether you think it's reasonable to incorporate it into decision-making?

DR RAVDIN: They did a really beautiful piece of work. They developed a 16-gene RT-PCR assay that measures several genes of interest in patients who are node-negative, estrogen receptor-positive. They actually developed and validated the assay in patients who had uniformly received tamoxifen, so the clinical questions the test was developed for are, "For node-negative patients who are estrogen receptor-positive, who will be receiving some form of hormonal therapy, what is their residual risk after that hormonal therapy, and is that residual risk substantial enough to justify the consideration of chemotherapy?"

The test is really paradigm-shifting because for the first time we have a strong multigene test. They developed it in the right way, using banked clinical trial specimens for which we have more than 10 years of follow-up. Their validation study had 675 patients, so they have a large set of patients with substantial follow-up. The test hasn't been immediately adopted by everyone because it still hasn't been published, and in some cases it hasn't been completely worked out. I think it's something that's slowly coming in, and it'll be interesting to see what additional data become available.

DR LOVE: Tom, can you follow up on what happened to this woman?

DR CARTWRIGHT: The Onco*type* DX™ assay was useful in this patient. She was at a relatively low risk for recurrence after receiving endocrine therapy. I wouldn't say I could recommend or not recommend chemotherapy to her. I left the decision up to her. Based on this test, she elected not to take chemotherapy. As a result, I put her on anastrozole. Her baseline bone density was normal.

DR LOVE: If this woman had a 20 to 30 percent risk of recurrence, do you think she may have opted for chemotherapy?

DR CARTWRIGHT: Yes. If her risk of recurrence was 20 or 30 percent with the anastrozole, I think she probably would have taken chemotherapy.

DR LOVE: Peter, what would your ADJUVANT! model say in terms of recurrence rate in this woman if she received tamoxifen versus anastrozole?

DR RAVDIN: For a node-negative patient, anastrozole makes the therapy proportionately better by about 10 percent. If her baseline risk had been 20 to 30 percent, the advantage of anastrozole over tamoxifen would be two to three percent, which is pretty close to the results of ATAC.

DR LOVE: I asked Gershon how, in general, he's managing patients like this. Peter, what happens when you see 100 women with node-positive, ER-positive tumors, in terms of how they are treated with hormonal therapy and chemotherapy?

DR RAVDIN: Of women with intermediate-risk, node-negative disease, about two-thirds receive some form of chemotherapy. Universally, if they're estrogen receptor-positive, they receive hormonal therapy. The aromatase inhibitors make that possible, even for some patients for whom tamoxifen is relatively contraindicated. We've all had patients who've had thromboembolic events and other issues, like endometrial cancer.

DR LOVE: In general, what do you usually recommend and what are the patients receiving as hormonal therapy?

DR RAVDIN: Currently, for patients whose disease is equivalent to Stage II node-negative or node-positive, I almost always recommend aromatase inhibitors if they're postmenopausal.

For patients with Stage I estrogen receptor-positive disease — except if they're at extremely low risk — I still recommend aromatase inhibitors. The few patients for whom I don't recommend an aromatase inhibitor are those who start out with osteoporosis.

DR LOVE: Dr Abel?

DR ABEL: I want to raise a question for which there is no answer. Is the patient going to have a more favorable experience with anastrozole or with tamoxifen followed by letrozole?

The other issue that Dr Locker raised is that the benefit from anastrozole over tamoxifen is equivalent to what might be gained with chemotherapy. If you were to give chemotherapy with anastrozole, you would have a further increment in benefit, which should be considered.

Another issue is that these tumors are close together. If serial sections were done, maybe they were bridged and there's one tumor, or if the molecular genetics were done, do the cells in between really have the changes of malignancy in them already? If so, maybe this really is one tumor rather than multiple tumors. This same risk consideration applies to colon cancers. How do you figure out the risk for multiple tumors?

DR LOVE: That's a great question. Dr Cartwright, where were these tumors in the breast?

DR CARTWRIGHT: All three of the tumors were in the same location. They were in the upper outer quadrant. One thing that's always confusing is, "Are they multicentric or multifocal?" Since they were all ER-positive, HER2-negative, Grade II, we assumed they were multifocal, or just one tumor that had spread through ducts rather than three separate multicentric tumors.

DR LOVE: The implicit question here is, "Is this really a three- or four-centimeter tumor?" Peter, my view is that your data in the ADJUVANT! program is based on actual SEER data, and because there are so few situations in which you have three one-centimeter tumors, I would imagine that we will never have "hard" data on cases like this one. Is that right?

DR RAVDIN: We really don't have exact numerical data about how to make estimates if you have a suggestion of multicentricity in a tumor. What I was suggesting earlier was that for relatively low-risk tumors it's pretty close to additive in terms of risk, so the fact that she had several of these tumors means it is going to push her toward the equivalent of a T2 tumor somewhere greater than two centimeters. She is certainly at a greater risk than a patient with Stage I breast cancer.

DR LOVE: I also want to address Dr Abel's question. Gershon, in the long run, would a patient like this — or any patient with an ER-positive tumor who is postmenopausal — be better off receiving tamoxifen followed by an aromatase inhibitor? But before we address that, do you think it's reasonable in a situation like this to utilize a test like Onco*type* DX™ to make a decision?

DR LOCKER: One of Dr Ravdin's many contributions to breast cancer treatment and research is his insistence on the distinction between prognostic and predictive tests. I've learned a lot from Peter about that. I am convinced that what we see here with this new test is prognostic, but we're using it to determine whether or not to give chemotherapy, and there is no predictive data. We don't know what the benefit of chemotherapy will be in patients who are at high risk based on this prognostic test. That's my concern. I'm convinced that it helps you prognostically, but I'm not ready to use it predictively. I'm curious as to what Peter would say about that.

DR RAVDIN: That is an important question because the test shows the residual risk, and it assumes that chemotherapy has the same probability of being effective or ineffective in

those women, as if they had never received tamoxifen.

In NSABP-B-20, half the patients received tamoxifen and the other half received CMF plus tamoxifen. I am curious as to whether or not Genomic Health is going back and evaluating the patients who received both chemotherapy and tamoxifen. That data would give us greater confidence that this test is, in fact, not only identifying people who are at risk for recurrence, but also patients for whom chemotherapy would actually make a positive difference. We don't know that yet. It's being assumed, but it would be nice to see the actual data developed to prove it.

DR LOVE: Gershon, can you address the other question by Dr Abel? In the long run, would patients be better off taking tamoxifen followed by an aromatase inhibitor? I think all the sequencing data has really sensitized us to the time course of recurrence and how much risk a woman is experiencing. How would you respond to that question?

DR LOCKER: The problem is, what are you going to tell the woman who was on tamoxifen in the first five years and relapsed because she wasn't on anastrozole in those first five years, or the women who had a DVT or a PE in those first five years, who wouldn't have had a DVT or a PE had they been on anastrozole?

Admittedly, the woman who doesn't have a fracture occur will be happy, but if she's going to get letrozole later on, she might develop a fracture.

That's with two years of anastrozole versus tamoxifen. The problem is that you can't start from the end of five years of tamoxifen. You have to start looking at events from day one, and there are a group of women who are going to have an adverse effect because they were on tamoxifen and not anastrozole for those five years.

DR LOVE: Dr Weiss?

DR WEISS: You're talking about using letrozole after five years of tamoxifen. Do we have any basis to say we should use five years of anastrozole versus 10 years versus indefinitely?

DR LOCKER: That's a great question. Last week there was a meeting of the ATAC investigators from the United States and Canada, and that was "the" question. What's the optimal duration?

Granted, anastrozole is better than tamoxifen, but for how long should it be administered? We were criticized for not writing that into the trial when the first results came out and, unfortunately, it was a technical issue of not being able to ask the question of five years versus 10 versus a longer duration.

The reason we're administering five years of aromatase inhibitors in all of these trials is based on tamoxifen data. It's somewhat naïve to assume that the two drugs may require the same duration of therapy. We don't know. It's a great question, and I wish someone would do the trial.

DR LOVE: Peter, what would you do in your practice if a woman who has just finished her fifth year of anastrozole walked into your office? Would you factor in the original risk the way you might as it relates to switching from tamoxifen to an aromatase inhibitor?

DR RAVDIN: At this time, many patients have a substantial risk of recurrence. It's important to point out that late recurrence includes, as defined in these trials, local and distant recurrence and a second primary event. Nonetheless, this risk is substantial — particularly in patients with Stage II disease. It's still even out beyond five years — approximately five percent per year.

A 40 percent reduction in risk is substantial, and these patients could benefit from an aromatase inhibitor. I usually explain that the data isn't as mature as we would like in that we have only three years of data, but it certainly looks positive. Those patients should certainly be offered an aromatase inhibitor, and it should be recommended to them. Patients with Stage II node-negative disease should also receive an aromatase inhibitor. I still have some question in my mind about whether patients who have had Stage I breast cancer in the past should receive an aromatase inhibitor.

DR LOVE: Dr Grabelsky?

DR GRABELSKY: I have computer screens in the exam rooms and I pull up the ADJUVANT! program and show it to patients. It's very nice when you see it in color on the screen. In general, when patients look at that small little sliver of effect chemotherapy has on overall survival, the majority of women say, "I'd rather not go through the side effects of chemotherapy for that small benefit."

If you present it as relative risk, more patients would accept it, but when you look at the absolute risk and you see it visually, I think that makes a big impact in how they come to their decisions.

DR LOVE: I have the sense that the culture of oncology has changed in the last few years, and I think a lot of it is from the ADJUVANT! model. Dr Grabelsky, I'm curious if you have changed the way you present this information to women.

DR GRABELSKY: In the past, I would just present the relative risk reduction. Now that we can present the information visually and see how small the absolute difference is, it has probably swayed how I present information and my own feelings about how important it is to recommend adjuvant chemotherapy in postmenopausal patients with node-negative, ER-positive disease.

DR LOCKER: It's laudable that in oncology we discuss absolute benefits. I think about other aspects of medicine. When we say statins save lives, we hear about the relative risk reduction of myocardial infarctions. Has anyone ever told us what the absolute risk reduction is from statins?

We're among the few medical professionals with hard numbers. But, as Dr Weiss said, we have to put the hard numbers into context and say, "Well, an absolute risk reduction of two percent means two people out of 100 won't be here in five or 10 years." However, when you're talking about mortality, a lot of toxicity is acceptable to patients.

DR LOVE: Dr Favis?

DR FAVIS: I think it's almost impossible to be completely unbiased in presenting this information.

I think patients pick up on subtle, subconscious clues, or they may ask you directly what you think. My paradigm has changed. I'm much more likely to suggest chemotherapy and aromatase inhibitors for many of these patients.

The other point is the chemotherapy we gave for Stage I breast cancer five or 10 years ago isn't the same as what we're giving now. I hear more and more researchers on the *Breast Cancer Update* audio series state that if they're going to give any chemotherapy, they want to give the best chemotherapy. We're widening the distance between the toxicity in both of those situations.

My default treatment is hormone therapy in these patients, unless there's information that the risk is much higher than I would be comfortable with. I've been choosing an aromatase inhibitor almost invariably, except in patients with known bone disease.

DR LOVE: I'm guessing the audio program you might be referring to was the recent one with Craig Henderson, who made the point that generally, when he uses chemotherapy in node-negative patients, he uses a taxane because he wants to use the one that's most effective. Peter, does that logic apply? Can we take the taxane data and apply it in terms of relative risk reduction to a node-negative patient?

DR RAVDIN: I think the answer is that we don't absolutely know because, of course, the trials have been done in patients with node-positive disease. The overview has always suggested that the proportional benefit of adjuvant chemotherapy is at least as large in node-negative disease as in node-positive disease. I think the logical extrapolation is to use the proportional benefit seen in the node-positive patients and carry it forth to the node-negative patients.

The other crucial bit of information — and I've actually discussed this with Craig Henderson — is that proportionately, classic chemotherapies like CMF and AC are less effective in postmenopausal patients than in premenopausal patients. However, an interesting effect was reported in the

overview that hasn't been commented on a lot, and that is that when you look at the advantage of anthracycline-based therapy, it's seen equally in premenopausal and postmenopausal patients.

The question I asked Craig Henderson was, "Did the addition of a taxane in trial 9344 have less of an effect in postmenopausal patients than in premenopausal patients?" In fact, it didn't. All of this supports the idea that we should consider using some of the more advanced chemotherapies in postmenopausal women.

DR JOSHUA: I agree with Dr Favis that patients take clues from us when we describe the advantages and disadvantages of therapy. Sometimes, as soon as the word chemotherapy is mentioned, they start shaking their head negatively. Obviously you're going to recommend more hormone therapy. We also take clues from our patients — it's hard to avoid that.

DR DRESDNER: On an opposite note, I've heard a surgeon say to the patient, "I'm sending you to the oncologist for chemotherapy," and when the oncologist tries to recommend hormone therapy, suddenly the patient doesn't understand why we're trying to give them less treatment than recommended by the other expert who just operated on them. It's a strange paradox when a patient actually asks for chemotherapy.

DR JOSHUA: Sometimes it's the other extreme, when the surgeon says, "All you're going to need is hormonal therapy," and then we're trying to explain to them, "No, you're going to need more than hormonal therapy."

DR LOVE: Dr Abel?

DR ABEL: You asked Steve earlier how oncology has changed. I think a very important change is that the oncologists and the patients are better informed as a consequence of having the ADJUVANT! program. Usually the pieces fall into place when you can show the patient the data. The decision becomes much easier and the absolute value demonstrated on the screen is a very effective way to present the data.

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Henderson IC et al. **Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer.** *J Clin Oncol* 2003;21(6):976-83. **Abstract**

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CASE 2: A 54-year-old Woman Seven Years After Node-positive (6/18), ER-positive, PR-negative Infiltrating Ductal Carcinoma (from the practice of Allan Freedman, MD)

- Right modified radical mastectomy and radiation therapy
- Received doxorubicin/cyclophosphamide
- Entered a clinical trial of myeloablative therapy with stem cell and bone marrow transplant
- Underwent STAMP-V therapy with failure to engraft and severe refractory pancytopenia, multiple infections and severe thrombocytopenia
- Completed five years of tamoxifen in 2002
- Patient has osteoporosis
- Patient recently refused letrozole and zoledronic acid

Key discussion point:

1 Aromatase inhibitors in patients at high risk completing five years of adjuvant tamoxifen

DR FREEDMAN: This patient is currently 54 years old, but she presented in December of 1996 at age 47 with an ER-positive, PR-negative infiltrating ductal carcinoma. She underwent a right modified radical mastectomy, and six of 18 lymph nodes were positive. At that time, we were collaborating with a local institution performing clinical trials with myeloablative therapy and stem cell and bone marrow transplant. She was entered into that study and was randomly assigned to four cycles of AC followed by STAMP-V myeloablative therapy and autologous bone marrow transplant. Subsequently she was going to receive tamoxifen following transplant.

She did very well with the adjuvant AC. Her marrow was harvested in September 1997 and evaluation of the bone marrow showed microscopic tumor but no evidence of metastatic disease by conventional scanning. She underwent STAMP-V therapy but, unfortunately, had a failure to engraft. She was left with severe refractory pancytopenia, which was complicated by multiple infections and severe thrombocytopenia, requiring platelet transfusions for several months. However, she did not have a relapse with her cancer.

She was started on tamoxifen and underwent a number of bone marrow biopsies during follow-up, which showed less than 10 percent cellularity. Her platelet counts were between 10,000 and 20,000.

DR LOVE: What was her menopausal status when she presented and when she began tamoxifen?

DR FREEDMAN: She was postmenopausal. In 2002, she was re-evaluated and had evidence of osteoporosis. She had finished five years of tamoxifen and I did not recommend continuing it, but I was very concerned about her future.

I offered her letrozole and zoledronic acid knowing that would be the only systemic therapy available to her if she were to relapse.

She had been traumatized by her prior therapy. In my practice, she's the only patient

I've ever had who's had a failure to engraft with any bone marrow transplant that we've ever been part of, and she would not consent to more therapy.

DR LOVE: What about your discussions after the MA17 data came out in November 2003?

DR FREEDMAN: I was even more strongly in favor of her going on letrozole. I told her she was at risk for a skeletal event but I was hoping that by using zoledronic acid we would be able to reduce her risk. I thought that risk was less than the chance she might die from breast cancer.

DR LOCKER: I think what you recommended is absolutely appropriate, and data support what you are doing, both in terms of the letrozole after five years of tamoxifen and that zoledronic acid would eliminate or lessen the risk of osteoporosis in this woman.

DR LOVE: Peter, what are your thoughts about the relative risks and benefits of an aromatase inhibitor at this point, one year after having stopped tamoxifen?

DR RAVDIN: I think that for a node-positive woman, particularly one who is estrogen receptor-positive, a fair amount of residual risk is present even beyond five years. Although there's a gap in her therapy, nobody has any idea whether or not that affects things. I think it probably doesn't.

DR LOVE: Regarding this issue of patients who've already stopped tamoxifen a year ago or five years ago, obviously we don't have definite information on that.

The most common response I've heard from the research community is to apply the relative risk reduction concept and assume that whatever the risk is at that point in time, you're going to reduce it. Peter, do you think that is a rational extrapolation at this point?

DR RAVDIN: I think the further out patients get, the lower the risk gets. I don't have any enthusiasm for broaching the topic of whether patients who stopped tamoxifen five years ago should start an aromatase inhibitor. I usually mention that information is available, but I don't recommend such treatment. It is much more of an issue for women who stopped their tamoxifen within the last couple of years, and I think it's reasonable to consider starting an aromatase inhibitor in those patients.

DR LOVE: Gershon, in general, when you see a woman who's been on tamoxifen for two to three years, how do you approach the issue of considering a switch to an aromatase inhibitor?

DR LOCKER: First you have to look at the risk. If a woman has multiple positive nodes, I discuss the two studies with two different aromatase inhibitors — exemestane and anastrozole — which demonstrate a benefit to switching at two to three years. I recommend it to women with node-positive disease.

The question is how this applies to patients with node-negative disease. In the Boccardo trial, which was the anastrozole switchover trial, all the women were node-positive. In the exemestane trial, about half of the patients were node-positive. Both of these studies were weighted towards women at higher risk. In women at lower risk, I present the data and say, "If you are comfortable on tamoxifen and you've had no positive nodes, fine." If they've had any issues at all with tamoxifen, they switch over to an aromatase inhibitor.

DR LOVE: Dr Favis?

DR FAVIS: We have all seen patients who perhaps had metastatic bone disease and did well on tamoxifen for over five years. I don't know what to do with those patients. I've been reluctant to discontinue it, and most of the patients have been reluctant to stop, too. I would have wondered, in your particular patient — when she refused to take an aromatase inhibitor — whether I would have just left her on the tamoxifen. There may not be much difference between your patient and somebody with known metastatic bone disease, except for maybe one log of tumor cells.

DR LOVE: That's a great point, particularly in view of the positive bone marrow.

DR FREEDMAN: I agonized over this and I felt that she was in an intermediate-risk group. We would all agree that she is a

ITA Trial: Anastrozole (A) versus Tamoxifen (T) in Women Already Receiving Adjuvant Tamoxifen (Median Follow-Up, 24 months)[1]

Treatment	Event-free survival		Progression-free survival	
	Hazard ratio	p-value	Hazard ratio	*p*-value
Tamoxifen (n=225)	1.0	0.0004	1.0	0.002
Anastrozole (n=223)	0.36 (95% CI 0.21-0.63)		0.35 (95% CI 0.18-0.69)	

"Conclusion: These findings confirm the role of A in the treatment of early breast cancer. Furthermore, the findings show that switching patients on adjuvant T to treatment with adjuvant A appears to decrease their risk of relapse and death. A was found to be more effective and induce less serious adverse effects than T in women already on treatment with this antiestrogen."[2]

SOURCES: [1]Boccardo F. Presentation. San Antonio Breast Cancer Symposium, 2003. [2]Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 3**.

patient with micrometastatic disease, yet technically, this is an adjuvant situation. I think if I had been enthusiastic about continuing tamoxifen, she would have continued it, but I had a hard time generating much enthusiasm for it.

DR RAVDIN: Is she already on a bisphosphonate?

DR FREEDMAN: No. She wouldn't take zoledronic acid, so I offerred her some of the other agents and she has decided not to take those either.

DR LOVE: You could also make the argument that she might potentially get a little tumor protection from a bisphosphonate. Peter, we have some randomized trials evaluating that question. What are your thoughts?

DR RAVDIN: The European data, at least from the largest trial, suggest that perhaps bisphosphonates will have an adjuvant effect. I think this is a fascinating area. It would be nice if bisphosphonates had an adjuvant effect, because that would strengthen the argument for the use of aromatase inhibitors. Right now, I'm not recommending bisphosphonates to my patients for their adjuvant effects, but I think there's going to be a lot more information of interest in this area.

DR LOVE: Another issue is which aromatase inhibitor should be used in which situation. Gershon, the most common answer I'm hearing from research leaders is whichever one had the supporting data: anastrozole up front, anastrozole or exemestane after two or three years, or letrozole after five years. Is that your approach?

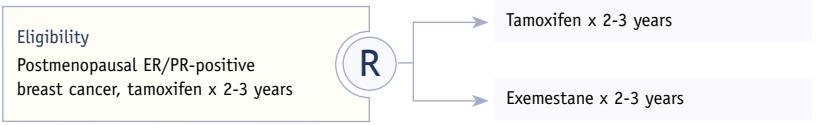
DR LOCKER: That is my approach. One question I ask is, "In patients you start on letrozole after five years of tamoxifen, for how long should they receive it?" The data was presented with a median of a little more than two years of follow-up, so do you treat them for five years? Do you treat them for two years? Do you treat them for three years? I don't have the foggiest idea.

DR RAVDIN: In all three of the large trials of aromatase inhibitors in early disease, the aromatase inhibitor clearly added benefit. I think all of these agents are going to be better than tamoxifen.

My guess is that the strategies we use will be based on the differential safety of these agents. They will possibly have different effects on bone density and other organs. In metastatic disease, there isn't a lot of difference between the efficacy of different hormonal therapies. We pick our therapy based on tolerability and safety. It'll be interesting to see the mature data from these studies, but I think they are all valuable

Phase III Randomized Study of Adjuvant Exemestane versus Tamoxifen

Protocol IDs: BIG 2-97, IBCSG 16-98
Accrual: 4,742 (Closed)



Hazard Ratios in the Exemestane Group as Compared with the Tamoxifen Group

Endpoint	Unadjusted hazard ratio (95% CI)	*p*-value
Disease-free survival	0.68 (0.56-0.82)	<.001
ER-positive	0.64 (0.52-0.79)	
ER-positive, progesterone-receptor-positive	0.66 (0.51-0.87)	
ER-positive, progesterone-receptor-negative	0.58 (0.38-0.90)	
Breast-cancer-free survival	0.63 (0.51-0.77)	<.001
Time to contralateral breast cancer	0.44 (0.20-0.98)	0.04
Overall survival	0.88 (0.67-1.16)	0.37

SOURCES: Coombes C et al. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92. Abstract. IBCSG website www.IBCSG.org/public/general-paper/trials/closed/trial-16-98-shtml

agents and are actually improving hormonal care.

DR LOVE: Gershon, there was a lot of discussion based on laboratory data that maybe exemestane was going to have a bone-sparing effect. What are your thoughts on that since the Coombes study came out?

DR LOCKER: I was disappointed, because in the metastatic setting one of the criteria for using exemestane was that it was better for bone. In the Coombes study, women who were switched to exemestane — and this was after having tamoxifen, so, theoretically, their bones were pretty well built-up — still had a trend toward osteoporosis and fractures. I'm concerned about that.

There are two explanations. One is that they were off of tamoxifen and it was the natural loss of bone in somebody who's not on a bone-protective agent. Given that this was seen within two years, I'm concerned that it's more than just natural bone loss because if you follow women over two years, you really shouldn't see that much bone loss.

The other argument is that it was borderline statistically significant. I'm disappointed because when you decrease estrogen levels in the body by whatever means, it isn't good for bone.

Comparison of Significantly Different Adverse Events between Exemestane and Tamoxifen

Type of event	Exemestane group	Tamoxifen group	*p*-value
	Any grade	Any grade	
Visual disturbances	7.4%	5.7%	0.04
Osteoporosis	7.4%	5.7%	0.05
Gynecologic symptoms	5.8%	9.0%	<0.001
Arthralgia	5.4%	3.6%	0.01
Diarrhea	4.3%	2.3%	<0.001
Vaginal bleeding	4.0%	5.5%	0.05
Cramps	2.8%	4.4%	<0.001
Thromboembolic events	1.3%	2.4%	0.007

SOURCE: Coombes C et al. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92. **Abstract**

Select publications

[1]Boccardo F. Presentation. San Antonio Breast Cancer Symposium, 2003. [2]Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 3**.

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Coombes RC et al. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92. **Abstract**

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Locker GY et al. **The time course of bone fractures observed in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2003;**Abstract 98**.

O'Regan RM et al. **Effects of raloxifene after tamoxifen on breast and endometrial tumor growth in athymic mice.** *J Natl Cancer Inst* 2002;94(4):274-83. **Abstract**

CASE 3: A 79-year-old Woman with ER-positive, PR-negative, HER2-Negative Metastatic Lobular Infiltrating Carcinoma and Malignant Ascites (from the Practice of Steven Weiss, MD)

- Presented in 1995 with a six-centimeter, node-positive (3/8) breast tumor
- Underwent mastectomy
- Tumor was ER-positive, PR-negative, HER2-negative
- Received tamoxifen but discontinued due to hot flashes
- Lost to medical follow-up
- Developed malignant ascites compatible with breast cancer recurrence

Key discussion points:

1. Management of patients resistant to treatment
2. Use of chemotherapy versus hormonal therapy to control malignant ascites
3. Role of tumor markers in following patients at high risk after adjuvant therapy

DR WEISS: My patient presented elsewhere in 1995 with a six-centimeter tumor, with three out of eight nodes positive. The tumor was estrogen receptor-positive, progesterone receptor-negative, HER2-negative. She underwent a mastectomy and received tamoxifen for a few months, but the tamoxifen caused hot flashes and she stopped it and was lost to medical follow-up.

DR LOVE: Do you have any more information about why, with this high-risk disease, she decided to stop tamoxifen?

DR WEISS: It didn't make her feel good. She didn't have any cancer present, and she didn't like to be bothered.

She hadn't seen any doctors during the intervening years, and she didn't like the medical structure in general.

She presented in August of 2002, seven years later at the age of 79, with malignant ascites. The ascites was tapped and proved to be an ER-positive, PR-negative adenocarcinoma, considered similar, morphologically, to her original disease. Her staging workup also had a small pleural-based density that might have been present in 1995, but we couldn't be sure. That was the first time I saw her.

I had actually seen her after the paracentesis was done. She was desperate about the shortness of breath and the amount of discomfort, and she wanted to do something to make sure it didn't recur. At that point, while in the hospital, she was receptive to just about anything.

DR LOVE: Do you think she would have accepted chemotherapy?

DR WEISS: Yes.

DR LOVE: Do you think she delayed coming in and was aware she had a problem?

DR WEISS: It was quite clear that she had it because this was not mild ascites. It had been developing for some time.

DR LOVE: Gershon, how would you have

thought through the options at that point? She's 79 years old, and it's seven years after her first diagnosis. It sounds like her main problem was ascites.

DR LOCKER: Was the histology lobular or ductal?

DR WEISS: It was lobular.

DR LOCKER: This is a very good story for lobular carcinoma, which can present as an "ovarian cancer wannabe" with ascites. The important thing is she had a long disease-free interval and was initially ER-positive. I'm not sure that chemotherapy would provide a higher likelihood of response than hormonal therapy, and it would certainly not give her as good a quality of life. I would consider her a good candidate for hormonal therapy, and I think this is a situation in which aromatase inhibitors might be ideal.

She didn't like tamoxifen, and although I suspect you could get her to take it again if you said it was the only alternative, we're talking about quality of life and patient preference in metastatic disease. For those reasons, I think she should go on an aromatase inhibitor.

DR LOVE: Steve, what about the issue of her compliance if put on an aromatase inhibitor? Would fulvestrant have been a consideration in terms of being more certain that she was receiving her therapy?

DR WEISS: At that point, her son was more involved, so compliance was less of an issue. Developing her trust and establishing a relationship was more essential at that time.

DR LOVE: Peter, how would you assess this situation in terms of chemotherapy versus hormonal therapy, and what type of each?

DR RAVDIN: I agree with Dr Locker. She had a long disease-free interval and really did not fail hormonal therapy in the past, and she's 79 years old. It's reasonable to start such a patient on hormonal therapy. I'm glad you've mentioned fulvestrant because this patient is of questionable medical compliance and with fulvestrant you can be sure she receives therapy. If she fails, you know it's not because of compliance issues.

DR LOVE: Gershon, what would be your assessment of the relative benefits in terms of antitumor effect in this situation — an aromatase inhibitor versus tamoxifen versus fulvestrant?

DR LOCKER: A lot of data suggest that an aromatase inhibitor is better than tamoxifen for first-line therapy for metastatic disease, depending on how you define benefit — whether it's duration of response, disease-free survival, et cetera. Several studies have evaluated these agents.

Generally fulvestrant and anastrozole are equally effective. However, in the study comparing fulvestrant and anastrozole, fulvestrant seemed to be most beneficial in patients with visceral disease, so I generally prefer fulvestrant in those patients. In patients who don't have visceral disease, either fulvestrant or anastrozole is acceptable.

DR LOVE: Could you elaborate more on those data in terms of response in patients with the visceral versus nonvisceral disease?

DR LOCKER: The overall results, which were published about a year ago, showed no significant difference between anastrozole and fulvestrant, but there were a few differences. Admittedly, these were subset analyses. The duration of response seemed to be longer in patients who responded to fulvestrant, and patients who had visceral disease seemed to respond better than those who did not. I think the takeaway message is they're equally efficacious; however, there may be subsets of patients in whom you might prefer to use fulvestrant, particularly those for whom compliance may be an issue or those with visceral disease.

The other important point is that other studies argue that you can use one and switch to the other. Third-line aromatase inhibitors are efficacious after fulvestrant and vice versa. These are more like anecdotal studies. In this woman, the reason I would choose the pills is that I think she may be more compliant because it may be less intrusive.

DR LOVE: She doesn't have bone metastases, so she's not coming in for a bisphosphonate

Combined Results from Two Multicenter Trials Comparing Fulvestrant to Anastrozole for the Treatment of Advanced Breast Cancer in Postmenopausal Women who Progressed on Prior Endocrine Therapy

Efficacy	**Fulvestrant n=428**	**Anastrozole n=423**
Objective response	19.2%	16.5%
Complete response	4.7%	2.6%
Partial response	14.5%	13.9%
Stable disease for ≥ 24 weeks	24.3%	24.3%
Median time to disease progression	5.5 months	4.1 months
Clinical benefit	43.5%	40.9%
Toxicity*	**Fulvestrant n=423**	**Anastrozole n=423**
Gastrointestinal disturbances**	46.3%	43.7%
Hot flashes	21.0%	20.6%
Joint disorders	5.4%	10.6%
Thromboembolic disease	3.5%	4.0%

*Percent of patients with predefined adverse events
**Gastrointestinal disturbances included anorexia, constipation, diarrhea, nausea and emesis.

SOURCE: Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38. Abstract

infusion every month, which may also be a consideration.

DR LOVE: Dr Cartwright, how would you have thought through this situation?

DR CARTWRIGHT: I would have considered giving her chemotherapy. Hormonal therapy takes six to 12 weeks to see a response with malignant ascites, and your chance of achieving a response is only 20 or 30 percent. You're going to have to be tapping her every week or so. If she were willing to take chemotherapy, I'd probably give her chemotherapy with the idea of switching her to hormonal therapy when the ascitic fluid is under control.

DR LOVE: Finally, we have a bit of controversy. Does anyone else have any thoughts in terms of chemotherapy versus hormonal therapy and type of hormonal therapy? Dr Freedman?

DR FREEDMAN: I would give her hormonal therapy. The things that influence me the most are her age, menopausal status, long disease-free interval, estrogen receptor status, the site of metastases and the fact that perhaps a malignant effusion is more like soft tissue and lymph node. I would use fulvestrant in this situation because I would be concerned about compliance and I wouldn't know if she was ever actually taking the anastrozole or letrozole.

I've also seen lobular carcinoma acting in a more aggressive fashion, and sometimes that influences me to recommend chemotherapy in an adjuvant situation in which maybe I

would only give hormonal therapy if it were a ductal carcinoma.

DR LOVE: Peter, this concept of compliance is one about which we haven't really seen a lot of literature. Ann Partridge from Dana Farber published a paper evaluating compliance with adjuvant tamoxifen, and it actually demonstrated significant noncompliance. What do we know from the medical literature about whether or not patients in this situation are reliable in terms of taking their medication?

DR RAVDIN: I can't definitively quote the medical literature, but it's certainly something to think about in patients who might have economic or social difficulties in getting their medicine. Although I've never seen this published, the half-life of tamoxifen is about a half a week to a week. If you miss a couple doses or even a couple days' worth of tamoxifen, it probably wouldn't affect your tamoxifen blood levels significantly. The half-life of aromatase inhibitors, however, is much shorter, so there is a possibility that if you were noncompliant you might lose a lot of the effectiveness of the aromatase inhibitors by taking them intermittently.

DR GRABELSKY: I probably would have chosen fulvestrant also. I'd be concerned about compliance issues, and you're going to be seeing this woman frequently, at least initially. In terms of traveling back and forth to receive the injection, I don't see that being a big hurdle. I know for our patients, the cost of prescription medications plays a role. Fulvestrant is covered by Medicare, whereas anastrozole and letrozole are not covered, and the patient would have to pay for them out of pocket. That is often an issue for my patients.

I've heard commentaries in the past about loading doses of fulvestrant. In this patient, for whom you're looking for a rapid response, is there any data about initially giving a more frequent schedule of fulvestrant to try to get a quicker response?

DR LOVE: Gershon, clinical trials are evaluating this concept of a loading dose of fulvestrant. What are your thoughts on that?

DR LOCKER: The original fulvestrant trial had a 125-milligram randomized arm that was stopped quickly because it was less efficacious, so we already have prospective data suggesting there may be a dose-response phenomenon. Whether it's a dose-response phenomenon or the need to load the tissues up is not clear, but this is under active investigation. This is still a work in progress but for now, 250 milligrams once a month is the standard dose.

DR LOVE: Dr Dresdner?

DR DRESDNER: The question is whether she'll show up for therapy. The injection is, at least, a good reason to bring her back to the office. Obviously, if her son is making decisions, compliance may be less of an issue, but in my own practice, patients sometimes just don't show up.

DR LOVE: Steve, can you give us a follow-up?

DR WEISS: By the time she showed up at my office a week after discharge from the hospital, her ascites was coming back fairly significantly. That pushed me toward using chemotherapy up front, and I started her on single-agent weekly paclitaxel. I gave her a total of 10 weekly doses and she had a rapid response with complete resolution of the ascites. However, her markers never really came down.

At that time she was significantly fatigued, but she was happy that the ascites wasn't coming back. I think that was the positive motivator for her to keep returning. We discussed the various options and I started her on letrozole, which produced a gradual decline in her tumor markers. By June 2003 it bottomed out at 112, then slowly began to climb back up, reaching the 500s by March 2004. She remained clinically asymptomatic with no more ascites.

DR LOVE: Do you think she was taking the pills?

DR WEISS: Yes; her son lived with her at that time, and she came to all her appointments. I have since become her primary care doctor. Surprisingly, she has towed the line pretty

Time Course of Bone Fractures in the ATAC Trial

"Six-monthly fracture rates… remained fairly constant for both A (range 0.93 to 1.57) and T (0.58 to 1.37), with the greatest difference between A and T seen at 18 and 24 mths. After 24 mths, the 6-monthly fracture rates seen with A reached a plateau. Overall osteoporotic fractures, encompassing sites of hip + spine + wrist, showed similar patterns. Anastrozole leads to an increased fracture incidence compared with T, a drug known to have a positive effect on bone. Importantly, the fracture rate in the A-treated group appeared to have stabilized after reaching a peak at 2 years."

A = anastrozole; T = tamoxifen

SOURCE: Locker GY et al. **The time course of bone fractures observed in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2003;**Abstract 98.**

well. She makes a lot of comments, but she does what she needs to do.

I restaged her: CAT scan, bone scan and PET scan were negative despite the high tumor marker, and she remained asymptomatic. Two months ago I started her on fulvestrant, and she is still asymptomatic.

DR LOVE: Gershon, would you have switched her therapy based purely on the tumor marker, even though the ascites resolved?

DR LOCKER: I probably wouldn't switch her therapy, but that may be a minority point of view. I generally don't use tumor markers to follow these patients because my view is that we're palliating the patient's symptoms. I'm not sure that early intervention in second- or third-line therapy translates into a survival advantage.

I just follow how the patient is doing. I can understand the argument for following tumor markers because you don't want to wait until her ascites recurs, but there is also the option of treating her the way you did before — with chemotherapy and then hormones. No, I wouldn't have switched her. I would have kept her on the aromatase inhibitor.

DR LOVE: Peter, you participated in another meeting we had in San Antonio about a year ago, and we had a "mini war" about the issue of tumor markers in metastatic disease. In a patient like this, who's clinically stable and in whom ascites has not recurred, do you think tumor markers should be an indication to switch therapy?

DR RAVDIN: I don't think we're absolutely compelled to follow tumor markers, because our major objective is palliation. If the patient doesn't have any symptoms, it's certainly reasonable to just follow her performance status.

I've found tumor markers advantageous when patients develop severe symptoms. If the markers go up, I tell the patient, "We could stay the course here." If the patient says, "I'm feeling great and I want to continue this therapy," I think it's reasonable to continue if you don't have any other evidence of disease progression. I use tumor markers to decide when to get radiology involved. For a patient like this, I probably would have been drawing markers. When you see three or four markers consistently going up, the physician and patient almost always decide to switch. I probably would have switched her, particularly when her tumor markers got so high.

DR LOVE: Dr Weiss, how is she tolerating the fulvestrant?

DR WEISS: She tolerated the fulvestrant without the slightest bit of difficulty. She is a thin woman, so we split the injections.

DR LOVE: You mentioned she had a pleural-based density. Has that changed during this time?

DR WEISS: I didn't see it in the last scans, so I'm assuming it was there and went away. It's below the sensitivity of a PET scan. I couldn't really call this measurable disease.

DR LOVE: I'm curious about your experience with a patient who's doing well with metastatic disease but has rising tumor markers. Dr Joshua?

DR JOSHUA: Most of the patients who are postmenopausal and have metastatic disease only in the bones, and the only other things we can follow on a regular basis are the tumor markers. It's very difficult in everyday practice to ignore the markers or tell the patient, "Yes, it has gone up by 100 points, but you're doing well. Let's continue the same treatment."

I have several patients like that, and they don't want to continue the same treatment. Every time I go to a meeting, I hear the experts saying, ignore the markers. When you go to the clinics, it's not easy.

DR LOVE: I love the dichotomy between research leaders and community practices. Dr Shah, what's your experience with this situation?

DR SHAH: If tumor markers go up and the patient is asymptomatic and the scans are stable, we have this discussion repeatedly, and I suggest a scan based on tumor markers. I scan them at that point to make sure there's no obvious disease progression. If there isn't, I don't change treatment.

DR FAVIS: When you originally started this patient on weekly paclitaxel, her ascites regressed but it didn't change the markers. The tumor markers don't seem to coincide with the amount of her disease.

DR LOVE: Is that something you've seen clinically?

DR FAVIS: To be perfectly honest, I almost never get tumor markers. I don't find them to be helpful.

DR WEISS: It's uncommon to see this dichotomy. We all have chronic lymphocytic leukemia patients and we watch their white counts go up, and we tell the patients, "Don't worry about a thing. We'll treat you when the time comes." Sometimes that works, but for other patients the fear of cancer, a painful bone metastases or another event is overwhelming. We have to accommodate those patients.

DR LOVE: We also have the issue of the family and a very involved son. Where do the two of them fit into this in terms of their approach? Are they calm or anxious about the markers?

DR WEISS: The son is a pleasure. He's very calm and willing to wait when we want, but the mother is upset. She's very afraid of the

2000 ASCO Tumor Marker Guidelines

"Further studies are required to determine whether the proposed greater sensitivity of the CA 27.29 assay will allow earlier determination of disease progression or will be achieved at the price of decreased specificity in the metastatic disease setting. …

"Routine use of CEA for monitoring response of metastatic disease to treatment is not recommended. However, in the absence of readily measurable disease, or an elevated MUC-1 marker (CA 15-3 and/or CA 27.29), a rising CEA may be used to suggest treatment failure."

SOURCE: Bast RC Jr et al. **2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology.** *J Clin Oncol* 2001;19(6):1865-78. **Abstract**

ascites, and it has become a very big issue for her. She does not want to have more problems with ascites for as long as possible.

DR LOVE: Did she ever express a sense of guilt or regret that she hadn't taken the tamoxifen?

DR WEISS: Not to me.

DR LOVE: Dr Grabelsky, is regret about earlier treatment decisions something you see in patients who have a recurrence with metastatic disease?

DR GRABELSKY: I have a personal experience in that regard. My mother had breast cancer and she relapsed nine years later. She received chemotherapy and tamoxifen but discontinued the tamoxifen after a very short period of time. When she relapsed, that was a big regret for her.

DR LOVE: A lot of times I wonder if patients have regret that we don't hear about because we don't ask about it. With your mother, you were very tuned into it. I wonder whether her physician was aware of how she felt.

DR GRABELSKY: I don't think he ever discussed that with her.

Case follow-up:

- Received single-agent weekly paclitaxel for 10 weeks
- Experienced complete resolution of the ascites but tumor markers remained elevated
- Began letrozole, which produced a gradual decline in her tumor markers
- Tumor markers gradually increasing again but remained asymptomatic with negative PET, bone and CAT scans
- Switched to fulvestrant

Select publications

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CASE 4: A 79-year-old Woman Presenting with a Palpable Five-centimeter, Node-positive (7/10), ER/PR-positive Lobular Carcinoma (from the Practice of Howard Abel, MD)

- Five-centimeter mass in the upper outer quadrant of the left breast
- ER-positive, PR-positive, node-positive (7/10)
- Invasive lobular carcinoma
- Underwent modified radical mastectomy (1-mm margin)
- Myocardial infarction more than 10 years ago

Key discussion points:

1. Adjuvant chemotherapy for elderly patients
2. Incorporation of ADJUVANT! into clinical practice
3. Selection of adjuvant hormonal therapy in patients with comorbidities
4. Quality control with ER testing

DR ABEL: This patient became aware of a palpable left breast abnormality in August 2003. Mammography demonstrated a mass in the upper outer quadrant. A core biopsy in late August identified an invasive lobular carcinoma. A left modified radical mastectomy in early October confirmed invasive lobular carcinoma, pleomorphic type, at least five centimeters at its greatest dimension. There was no vascular or perineural invasion, and the tumor extended to within one millimeter of an inked margin. The tumor is metastatic in seven of 10 axillary lymph nodes and is strongly positive for estrogen receptor and intermediately positive for progesterone receptors.

This woman is 79 years old and lives with her husband. Her performance status would probably be one, but her lifestyle would be characterized as limited because she was physically frail. Overall she was alert, conversant and pleasant.

In 1992 she sustained a myocardial infarction, and she is also symptomatic with a peripheral neuropathy.

DR LOVE: We've been talking about the different perspectives that patients and doctors have on adjuvant therapy. Some patients want everything possible, and others are more conservative. Where does this woman fit in?

DR ABEL: We consulted ADJUVANT! and I showed her the graphic representation of the results. It became very clear that chemotherapy was not worth pursuing. She had comorbidities in terms of peripheral neuropathy and ischemic cardiac disease, so the administration of chemotherapy would have been problematic.

DR FOX: I think most of us try to begin with a big-picture view of a woman's options. In our practice, we use Dr Ravdin's program fairly often. I don't know that I would

use it for this case because the issues become somewhat self-evident due to the comorbidities.

I always return to the Oxford overview, as it continues to remind us that the worth of chemotherapy in reducing the risk of dying from breast cancer always seems to be diminished in the older patient relative to the younger one.

In cases like this, I think most of us quickly develop a bias. We'd rather not give this woman chemotherapy for a whole lot of reasons, but even in a healthy 79-year-old the benefit is going to be somewhat attenuated relative to someone who is 39.

In this frail, nearly 80-year-old woman with comorbidities, I can't envision the worth of any chemotherapy regimen. You've given very good reasons not to give this woman a taxane-based therapy. You've given fairly good reasons to be concerned about anthracycline-based therapy.

That leaves us with CMF. If you look hard at the contribution of CMF to the outcome in older patients, it's rather meager in the context of estrogen receptor-positive disease when you have tamoxifen, aromatase inhibitors or both. I would not give chemotherapy to this woman.

DR LOVE: If this woman was extremely healthy without any comorbid illnesses, would that change your approach?

DR ELLEDGE: I don't think it would change much. When I explain to patients the decision between hormonal therapy or combination hormonal/chemotherapy, I make it very clear that hormonal therapy is more important, so that they don't agonize too much over this decision.

Many patients feel that chemotherapy is more important, but in receptor-positive disease you generally get twice the benefit from hormonal therapy. I think the bottom line is that I would still recommend hormonal therapy alone.

The choice of hormonal therapy is tougher because there are pros and cons to both tamoxifen and aromatase inhibitors. With tamoxifen, clotting events are age-related, so I would say that a person like this has a clotting event risk over a five-year period of about two to three percent, which is pretty high. On the other hand, aromatase inhibitors have osteoporotic risk.

DR LOVE: One of the things I've always liked about the Ravdin model is that it takes age and comorbid illness into consideration and as you start looking at the numbers, the benefit of therapy is diluted out. What numbers did you derive in this case, and what happened with your discussion concerning choice of therapy?

DR ABEL: With no additional therapy, only one out of 100 women would be alive and without cancer at 10 years; 37 out of 100 would relapse, and 62 out of 100 would die of other causes. That's compelling. With hormonal therapy, you salvage two patients out of 100, whereas with chemotherapy, you salvage less than one out of 100. I showed the patient these numbers and the decision fell into place immediately. The conclusion was obvious that the only way to intervene here was with hormonal therapy. The website indicated a marginal benefit for anastrozole versus tamoxifen, so she started anastrozole as systemic treatment and has tolerated it uneventfully.

DR LOVE: What has been your experience using adjuvant chemotherapy and hormonal therapy in elderly patients?

DR WEISS: In a very healthy elderly person I would consider it, and the debate is not for a 10-year benefit as much as for a five-year benefit. In the person who has other comorbidities and a lower probability of five-year survival, the sacrifice of a half year, even if she were to make it through well, becomes more problematic.

We see an increase in strokes and in the risk of thrombotic events with tamoxifen, and I am beginning to question whether tamoxifen should be used in this population.

When we use aromatase inhibitors, we can treat osteoporosis. Unless I see someone with severe, unresponsive osteoporosis, my

inclination in the older patient is to treat with an aromatase inhibitor.

DR FAVIS: I agree with the consensus and would not have encouraged chemotherapy. However, in the rare patient who demands it or might derive some benefit from it, I have occasionally used capecitabine. If you are careful with it, I think you have a lot less trouble than with CMF, AC or practically anything else.

DR LOVE: A trial is comparing capecitabine to AC and CMF in elderly people. Richard, what are you doing about the patient with an ER-negative tumor who is 75, 80 or 85 years old?

DR ELLEDGE: Certainly chemotherapy is not as well-tolerated. There is no real cut point, but I give chemotherapy to a few patients who are in their seventies and I see a lot more problems in this age group. I frequently use AC, and even with that I see more problems.

DR LOVE: What can we expect the incidence of ER-positivity to be in a 79-year-old woman using Craig Allred's definition of any cells being positive?

DR ELLEDGE: If we discard the lobular histology, it's more than 80 percent. Lobular histology will drive it up higher, approaching 90 percent. In Europe and the United States, when you do tight quality control at central labs, approximately 20 percent of tumors that are classified as ER-negative will come back positive, so I always retest all ER-negative tumors.

My only other comment is that I agree with your choice of anastrozole. Sometimes we waffle around in these discussions and don't actually say what we would do.

DR LOVE: Richard, you say that sometimes people waffle about choice of hormonal therapy. Are you more inclined toward anastrozole in a HER2-positive patient?

DR ELLEDGE: We have two sets of data that are criticized for being small sets, but they are actually quite consistent and are independent. They show that if you have overexpression of the HER family of receptors, for whatever reason, the aromatase inhibitors are more effective than tamoxifen.

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CASE 5: A 35-year-old Woman with a Strong Family History of Breast Cancer with Comedo DCIS Followed by Infiltrating Ductal Carcinoma Three Years Later (from the Practice of Stephen Grabelsky, MD)

- Mammogram revealed a cluster of microcalcifications in the right breast
- Stereotactic biopsy revealed comedo DCIS
- Re-excision was negative for residual disease
- Underwent lumpectomy, radiation therapy and tamoxifen therapy
- Three years later while on tamoxifen, developed an ER/PR-positive, HER2-negative, 1.0-centimeter, moderately differentiated infiltrating ductal carcinoma in the same breast

Key discussion points:

1. Management of the premenopausal patient with an ER-positive tumor
2. Genetic testing for BRCA-1 and BRCA-2
3. Maintaining fertility after ovarian suppression
4. Use of hormonal therapy for DCIS

DR GRABELSKY: The patient is a 35-year-old married woman with two children and a strong family history of breast cancer. Her mother had breast cancer, a maternal aunt had ovarian cancer, and a maternal first cousin had bilateral breast cancer. Because of her family history she had early mammograms, one of which showed a cluster of microcalcifications within the right breast. A stereotactic biopsy revealed intraductal carcinoma with comedo necrosis. She underwent re-excision, which revealed no residual intraductal carcinoma. She received radiation therapy and was placed on tamoxifen at that time.

She did well for three years, until routine follow-up mammography revealed a new lesion in a different quadrant of the same breast. She underwent a biopsy, which revealed a 1.0-centimeter, moderately differentiated infiltrating ductal carcinoma. An axillary lymph node dissection revealed 13 negative lymph nodes. Estrogen receptors were 95 percent and progesterone receptors were 90 percent. HER2 was negative by immunohistochemistry.

DR LOVE: Incidentally, was she Jewish, and did the subject of genetic testing come up?

DR GRABELSKY: Yes, and there were some concerns on her part about testing because of insurance issues. Because of the strong family history, she elected to have bilateral mastectomies and an oophorectomy.

DR LOVE: Let's talk about management of this premenopausal woman. Kevin, how would you think this through?

DR FOX: The case would be much more difficult had she not decided to have an

oophorectomy. Let's assume for a minute that she chose not to. Here you have a young woman with a relatively low-risk cancer. I think most of us would consider systemic chemotherapy and hormonal therapy as each would contribute a modest amount to reducing her risk of dying of breast cancer.

The choice of chemotherapies is relatively straightforward — it's pretty much whatever you want it to be. I think most of us would probably use AC. Fortunately or unfortunately, a 35-year-old woman does not stand an overwhelmingly high chance of going into menopause with AC, so let's assume she retains her menstrual function, with a tamoxifen-resistant cancer. My own bias — although I've never actually done this — would be to induce ovarian failure with medical oophorectomy and utilize an aromatase inhibitor.

DR ELLEDGE: I think the answer to the question, "Does oophorectomy add to tamoxifen in premenopausal patients?" is still out there. We have a large international trial addressing that very issue, but everything we know about estrogen, breast cancer and the interaction of a ligand with its receptor in an environment of high estrogen would suggest that it would be better to have low amounts of estrogen.

We still need to do a trial to prove that, but I am very nervous when I have a multiple node-positive patient who is premenopausal, ER-positive and not rendered amenorrheic by chemotherapy. I have induced menopause in a very small number of these patients. It has not been more than five in the last five years, but I have done it.

DR LOVE: The other issue is patient attitude. Can you talk more about her thoughts about chemotherapy?

DR GRABELSKY: In addition to being a full-time mother, she is an aerobics instructor and personal trainer. We had a long discussion, and she was very concerned about body image and the side effects of chemotherapy. We talked about what might happen if she remained premenopausal versus undergoing surgical oophorectomy and what the implications were for hormonal therapy versus chemotherapy.

After she underwent the oophorectomy, we again discussed the additional merits of chemotherapy in a one-centimeter, Grade II, strongly ER/PR-positive, HER2-negative tumor. She was fairly adamant about not receiving chemotherapy, and we elected to treat her with anastrozole alone.

DR LOVE: Kevin, when we talk about management of premenopausal patients, particularly those who want to have children in the future, your name often comes up for some of the innovative work you've done. Can you update us on that?

Ongoing Trials of Adjuvant Endocrine Therapy in Premenopausal Patients

Study	Entry Criteria	Intervention	Target Accrual
ABCSG-AU12	Stage I, II	Tamoxifen + goserelin ± zoledronate Anastrozole + goserelin ± zoledronate	1,250
IBCSG-24-02	T1-T3, pN0-N2	Tamoxifen Ovarian suppression + tamoxifen Ovarian suppression + exemestane	3,000
IBCSG-25-02	T1-T3, pN0-N2	Triptorelin + tamoxifen Triptorelin + exemestane	1,845
IBCSG-26-02	T1-T3, pN0-N2	Ovarian suppression + tamoxifen or exemestane Ovarian suppression + chemotherapy + tamoxifen or exemestane after chemotherapy	1,750

DERIVED FROM: NCI Physician Data Query, June 2004

DR FOX: Based on some suggestive information from Hodgkin's disease, we utilized ovarian suppression concurrent with chemotherapy in about 30 patients in an attempt to protect their ovaries from the cytotoxic effects of the chemotherapy. The primary intent of this project was to see if we could preserve menstrual function and document how many women retained their ability to have cyclic menses upon the completion of chemotherapy. The secondary intent was, of course, something that is much harder to measure — fertility.

We found that we were able to retain menstrual function in 29 out of 30 patients. It is remarkable that if you give a woman three or six months of leuprolide acetate or goserelin, she will stop having menses and then, almost predictably, resume having them in about six months.

That was fine until we began to look at fertility outcomes over the next few yeas. I found the results very discouraging. Of the 30 patients evaluated, 11 claimed to be actively attempting to become pregnant. Five of these women were able to get pregnant but only two were successful without infertility treatment. Overall, there were six pregnancies but only two successful births.

You can look at this in many ways. First, the number of patients is too small to draw any sweeping conclusions. However, when we saw how difficult it was for these patients to become pregnant, we began to ask whether we were doing them any good. The cooperative groups have taken a larger interest in this project, which I think is good, but in my opinion, continuing it in a single-institution fashion was less than responsible.

The second problem is that the estrogen receptor-positive women, which constituted just over half of our patient cohort, under many circumstances would not take the tamoxifen that was being recommended to them because they intended to become pregnant. In our cohort of 30 patients, six relapsed, four of whom were ER-positive women and had declined tamoxifen. To me, that was an even more troubling aspect of this effort, and we no longer do this outside of a clinical protocol.

DR LOVE: If this woman had decided to undergo genetic testing and was found to be negative or had decided not to have her ovaries taken out, would that have changed your approach to this situation?

DR FOX: I have developed a healthy respect and distrust for BRCA-1 and BRCA-2 in terms of what they mean to patients who are not carriers of identifiable mutations. This woman is Jewish, and her family history hints at something that is genetically driven. If she were not a mutation carrier by current identification, I would not have discouraged her from having prophylactic surgery.

As far as her ovarian function, I would have induced menopause medically in order to justify the use of an aromatase inhibitor, which would be her best therapeutic option in the context of tamoxifen resistance.

DR ELLEDGE: I would have strongly recommended that she have a genetic evaluation even if she did not want genetic testing. Our genetics counselor will take an entire family pedigree, put it into a computer, and estimate the probability of a BRCA-1 or BRCA-2 mutation. With this family history, our model would spit out a number that approaches 100 percent in terms of a BRCA-1 or BRCA-2 mutation.

Testing in the Ashkenazi Jewish population is more technically straightforward, and I would have recommended that she have an Ashkenazi Jewish panel performed. I think that it would have been positive, probably for BRCA-2. It doesn't sound like it would have changed anything that she did, but it would allow other family members to make important decisions.

DR GRABELSKY: In regard to Richard's point, she actually did seek genetic counseling and they felt that there was a high likelihood that she would test positive. As soon as her insurance situation stabilizes, she intends to be tested because she has a daughter.

DR ELLEDGE: Just as a practical point, I tell my patients it is illegal to discriminate

against a person on the basis of a genetic test either for insurance premiums or for employability.

DR LOVE: Kevin, this case also brings up the issue of hormonal therapy in DCIS, as this woman broke through her treatment with tamoxifen. In this case it was an invasive recurrence, but about half of the recurrences are recurrent DCIS. Can you talk about your approach to hormonal therapy for DCIS and particularly the woman who progresses on tamoxifen?

DR FOX: The current clinical trial of tamoxifen versus anastrozole in DCIS is predicated on the presence of estrogen receptor, so a default position has been taken that tamoxifen or anastrozole cannot possibly work if the patient's DCIS does not express estrogen receptor. Although I think it is intuitively obvious that that should be the case, are mechanisms at play here that guarantee tamoxifen to be worthless in a woman whose DCIS is ER-negative?

DR LOVE: So, you are concerned that maybe there is benefit in women who are ER-negative. The other thing that you might want to comment on, Rich, is that women who are called ER-negative in the community actually did benefit because there were so many false negatives.

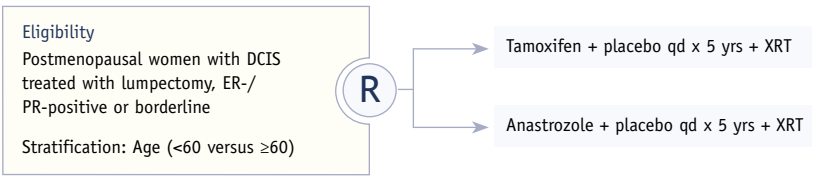
DR ELLEDGE: Using Craig Allred's technique as the gold standard — and it's been validated to be accurate in a number of clinical trials — there is a 50 percent misclassification for estrogen receptor status in DCIS in his study of 400 patients. Unfortunately, it was a coin flip as to the estrogen receptor status. His evaluation detected no benefit in ER-negative DCIS, which goes along with what we see in invasive breast cancer. The data is not strong in terms of statistical stability, but it's backed up by a lot of biology. It needs to be confirmed in another study, but I'd be surprised if it was wrong.

DR ABEL: How should we handle an ER-negative DCIS case in the community? We probably do not have the luxury of getting repeat testing done through the insurance companies. Shall we assume they are all positive?

DR ELLEDGE: No. I do not think so, because doing so would subject your patient to five years of a drug with significant cost and potential side effects. What you can do is look at the lab where your sample was tested. If it is one of the larger central labs, you can have more confidence. I really get nervous about smaller individual hospitals because that is where the mistakes are made.

NSABP-B-35: Tamoxifen versus anastrozole in Postmenopausal Patients with Ductal Carcinoma in Situ — Open Protocol

Accrual: 3,000 pts.



Study Contact: Richard Margolese, Chair
National Surgical Adjuvant Breast and Bowel Project
Tel: 514-342-3504

SOURCE: NCI physician Data Query, June 2004

Select publications

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Baum M, O'Shaughnessy JA. **Management of premenopausal women with early-stage breast cancer: is there a role for ovarian suppression?** *Clin Breast Cancer* 2002;3(4):260-7. **Abstract**

Cuzick J. **Aromatase inhibitors in prevention--data from the ATAC (arimidex, tamoxifen alone or in combination) trial and the design of IBIS-II (the second International Breast Cancer Intervention Study).** *Recent Results Cancer Res* 2003;163:96-103. **Abstract**

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CASE 6: A 39-year-old Woman Presenting with Locally Advanced Breast Cancer and Diffuse Bony Metastases (from the Practice of Rajesh Bajaj, MD)

- Presents with a large central mass in her right breast with an inverted nipple and bulky nodes
- Experiencing generalized pain from diffuse bony metastases requiring narcotics
- Elevated CA27-29
- Biopsy revealed an ER/PR-positive, HER2-negative infiltrating ductal carcinoma

Key discussion points:

1. Management of the premenopausal patient with ER-positive metastatic disease
2. Ovarian suppression plus hormonal therapy for metastatic disease
3. Mastectomy and breast reconstruction for the young patient with metastatic disease

DR BAJAJ: This patient was a relatively healthy 39-year-old married computer technician with no children. When she presented she had a rather obvious large central mass occupying most of her right breast. Her nipple was inverted, and there were also bulky nodes in the axilla. She having generalized pain, which she thought was musculoskeletal but turned out to be the result of diffuse bony metastases. Most of her bones were involved on the bone scan, and her alkaline phosphatase was about 800. Her CA27-29 was elevated and her performance status was one. There was no one site that hurt her the most, but she needed narcotics for pain control. Her biopsy revealed an infiltrating ductal carcinoma that was ER/PR-positive and HER2-negative.

DR FOX: This is a case for which I would not necessarily rely on hormonal therapy as my first intervention, simply because it could take several weeks for her to respond to hormonal therapy. With a patient who requires a narcotic for pain, leapfrogging right to systemic chemotherapy with a doxorubicin-based regimen for a short time might be the responsible thing to do.

Response rates among different anthracycline-based regimens as first-line therapy don't differ much. If our objective is to give her the greatest degree of pain relief, we should probably seek something that has a legitimately high risk of response, such as doxorubicin/cyclophosphamide or doxorubicin/docetaxel. This would not be a long-term plan. It would be enough to make her feel better and then switch to some form of hormonal intervention, which in this case should probably be ovarian ablation.

DR ELLEDGE: She has a large amount of bulky disease, which influences my decision. I'd recommend hormonal therapy up front in this case. Because the tumor was strongly ER and PR positive, she has a high likelihood of response. Our neoadjuvant studies with aromatase inhibitors have a response rate

of 60 percent. If she didn't have bulky disease, I would consider an LHRH agonist and tamoxifen as initial therapy. If she had a really large tumor, I might consider chemotherapy. With this type of case, being at the bedside would help my decision.

DR LOVE: Let's hear more about the bedside. What went on in your discussions with her, and what did you decide to do?

DR BAJAJ: I staged her and looked for metastatic disease, and there were no other sites of metastases. She had locally-advanced breast cancer and diffuse bony metastases, which were controlled with an analgesic. At that point I decided to start her on tamoxifen for about two to three months; then I added goserelin. She was slowly getting better. Her breast mass slowly decreased, her pain was controlled and her tumor markers started to come down after about three months, so we continued this combination.

She basically had a continued slow response over six months with this combination treatment. I was able to get her off the narcotics completely, and she remained narcotic-free for about 18 months after that.

In the meantime, I was concerned about her locally advanced disease, so about nine months into treatment, when she was in remission, I sent her for a toilet mastectomy. There was a significant amount of tumor in the central part of her breast, with multiple positive nodes. The margins came back negative and she chose to have immediate reconstructive surgery. In fact, she had her other breast enlarged at the same time. That's what she wanted, so I did not object to it. After surgery she underwent radiation to the chest wall.

DR LOVE: What was the cosmetic outcome, and how was her quality of life at that point?

DR BAJAJ: It was fine. There was no complication. She was working full-time, off narcotics and fully functional. Her tumor markers came down quite a bit but never really normalized. Slowly, over the past six months, they have started to go back up. She was asymptomatic and started to have pain again. This past December we switched her to anastrozole because she was having more pain and rising tumor markers. I continued the goserelin and zoledronic acid.

DR ELLEDGE: That is exactly what I would have done. I would have performed a toilet mastectomy on this patient for a couple of reasons. This woman has basically neglected an ER-positive breast cancer that she could live with for many years. She has no visceral metastases and has bulky disease. If it got out of control, radiation therapy would not handle it, so I would have done exactly the same thing.

In terms of reconstruction, I have had one patient, a very young woman in her twenties with metastatic disease, who strongly wanted reconstruction. Her disease was controlled and she had an implant reconstruction. I went along with it but would not agree to a TRAM flap.

DR LOVE: Kevin, earlier you said you have not used ovarian suppression plus an aromatase inhibitor in the adjuvant setting. What about that same strategy in metastatic disease?

DR FOX: In this case, I think it makes the most sense as a backup plan in case the combination of the LHRH agonist and tamoxifen fails. We have done that plenty of times, mostly in patients who are already ovarian ablated or suppressed in whom the change to an aromatase inhibitor is just natural.

DR FAVIS: I'm a little perplexed. If you're going to give her an LHRH agonist and make her postmenopausal anyway, why give her tamoxifen when you know that an aromatase inhibitor is actually a better drug?

DR FOX: That's a very good question. Without meaning to be cynical, the choice of first-line therapy is not terribly important as long as we feel she is going to respond to it. There is probably an additive response by giving ovarian suppression and tamoxifen or an aromatase inhibitor over ovarian suppression alone. However, it is really the sequence of therapies that is going to matter in the end. I would take it one step further and say it would also be justifiable to give her ovarian suppression by itself.

DR LOVE: Richard, what would you do if this woman has a good response to the anastrozole and LHRH agonist and then progresses? Again, she has no life-threatening disease.

DR ELLEDGE: I would consider fulvestrant or a different class of aromatase inhibitor. Lacking any objective data, I'd probably continue the LHRH agonist.

DR FOX: Most of what we know about these compounds comes from their use in endometriosis. Young women have a remarkable ability to resume normal menstrual function even after receiving this agent for a year or two, so I would agree to continue administering it.

DR ELLEDGE: In order to provide some controversy, if she responded and failed a different aromatase inhibitor or fulvestrant, I might come back with five days of DES three times a day. I think that using high-dose estrogens to change the estrogen environment as much as possible is quite toxic to breast cancer cells.

DR LOVE: Kevin, have you done that recently?

DR FOX: No, but I like the idea.

DR LOVE: In a premenopausal woman?

DR ELLEDGE: I wouldn't do that in a premenopausal woman, but this patient has been postmenopausal for a couple years.

DR LOVE: You said you'd stop the LHRH agonist?

DR ELLEDGE: Yes, I would stop the LHRH agonist when I went from below postmenopausal levels of estrogen to high-dose estrogen. Giving high-dose estrogen to premenopausal women is ineffective.

DR ABEL: Can you obtain DES these days?

DR ELLEDGE: You can, but it has to be compounded. For a while, I used Premarin®, but was very uncomfortable with that because I really did not know the dose. Most large cities have a compounding pharmacy that can compound it at five milligrams TID. I see a couple of patients a year who come to me for second opinions after having three, four or five hormones. I put them on DES, they respond and feel good, and I look like a genius.

Case follow-up:

- Treated with goserelin plus tamoxifen and zoledronic acid
- Breast cancer mass decreased
- Tumor markers declined
- Underwent a toilet mastectomy revealing multiple positive nodes, immediate reconstructive surgery and radiation therapy to the chest wall
- Patient remained narcotic-free for 18 months

Select publications

Baum M, O'Shaughnessy JA. **Management of premenopausal women with early-stage breast cancer: is there a role for ovarian suppression?** *Clin Breast Cancer* 2002;3(4):260-7. **Abstract**

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Fogelman I et al. **Bone mineral density in premenopausal women treated for node-positive early breast cancer with 2 years of goserelin or 6 months of cyclophosphamide, methotrexate and 5-fluorouracil (CMF).** *Osteoporos Int* 2003;14(12):1001-6. **Abstract**

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Jakesz R et al. **Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5.** *J Clin Oncol* 2002;20(24):4621-7. **Abstract**

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Sainsbury R. **Ovarian ablation in the adjuvant treatment of premenopausal and perimenopausal breast cancer.** *Br J Surg* 2003;90(5):517-26. **Abstract**

CASE 7: A 70-year-old Woman with ER-positive, HER2-negative Metastatic Lobular Carcinoma to the Bone, Liver and Soft Tissue of the Orbit (from the Practice of Richard Levine, MD)

- Biopsy of the upper inner quadrant of her right breast 12 years ago revealed a 4x3x3-centimeter infiltrating lobular carcinoma
- ER-positive, PR-negative tumor
- Node-positive (1/9)
- Underwent breast-conserving surgery with clear margins and radiation therapy
- Received CMF x 6 and tamoxifen x two years, discontinued due to macular degeneration
- Follow-up 12 years later revealed anemia, elevated CA27-29
- Bone scan and X-ray revealed skeletal and liver metastases
- HER2-negative by IHC and FISH

Key discussion points:

1. Sequencing endocrine therapy in the metastatic setting
2. Treatment of the patient with ER-positive asymptomatic metastatic disease
3. Potential benefits of parenteral therapies
4. Combining hormonal therapy with biologic agents

DR LEVINE: I first saw this patient in 1988 when she was 56 years old. She was a recovery room nurse who noted a lump in the upper inner quadrant of her right breast. A biopsy revealed infiltrating lobular carcinoma. It was 4x3x3 centimeters, and one of nine nodes were positive. She underwent breast-conserving surgery and her tumor margins were negative. Her tumor was ER-positive at 9.5 and PR-negative. She was treated with six courses of CMF, breast irradiation and tamoxifen.

She discontinued the tamoxifen after two years because she had macular degeneration and was concerned that this was the result of the tamoxifen.

The patient remained disease-free and returned for follow-up once a year. She took a bicycle trip around the world for 12 months in 2000. When she came back, which was about a year and a half after her last visit in February 2001, she was anemic, with hemoglobin of 10 and an elevated CA27-29. I did a metastatic work-up and everything was negative other than her bone scan and a subcentimeter lesion in her liver. X-rays were also compatible with metastatic disease of the skeletal system. Mammogram was negative. Bone marrow biopsy revealed extensive involvement of metastatic

adenocarcinoma consistent with lobular carcinoma of the breast. HER2 was negative by IHC and FISH.

DR LOVE: Can you talk about what her clinical status was at that point? What was her attitude, her family support, et cetera?

DR LEVINE: She is a very active, otherwise healthy person. She had no history of smoking or alcohol use. Her performance status was 100 percent. She bicycled around the world with her husband and had a very good support system and a very athletic family.

DR LOVE: Richard, this woman is presenting with anemia, bone and bone marrow metastases and a liver lesion, but she is completely asymptomatic and very active. She has had two years of tamoxifen and then an ophthalmic problem. With that said, how would you approach her systemic therapy at that point?

DR ELLEDGE: She has a long disease-free interval and we're not sure but she probably has bone-only disease. She has few, if any, symptoms, and estrogen receptor-positive disease, so she is an ideal candidate for hormonal therapy. In this case, I would start with an aromatase inhibitor, but you could start with tamoxifen or fulvestrant.

DR LOVE: In a situation like this one, how would you select hormonal therapy? Any thoughts about the increased duration of response with fulvestrant?

DR ELLEDGE: That was seen in one study. It's an interesting observation but I wouldn't use it to make a therapeutic decision. I consider the side-effect profile, ease of administration and therapeutic efficacy. The aromatase inhibitors have demonstrated a small response and progression-free survival advantage to tamoxifen, so I would pick an aromatase inhibitor because they are easy to take, have few side effects and are probably the best in terms of therapeutic efficacy.

DR LOVE: I'm certain this woman was receiving bisphosphonates. Kevin, does the fact that the woman is coming into the office every month and could easily get an intramuscular (IM) injection at that time affect your choice between an aromatase inhibitor and fulvestrant?

DR FOX: The reasons to use fulvestrant in this situation would be economic or if there were a question about compliance. It doesn't sound like either would be an issue in this case. She happened to be coming in on a monthly basis, but that alone wouldn't provoke me to choose fulvestrant.

DR FAVIS: Wasn't there a study comparing tamoxifen to fulvestrant in the first-line setting that showed tamoxifen to be better?

DR ELLEDGE: No, that perception is not true. If you look at the data recently published in the *Journal of Clinical Oncology* in the ER-positive subset, fulvestrant and tamoxifen were basically equivalent. If you evaluate all the patients, there was some numerical inferiority for fulvestrant.

One factor you might consider in selecting a hormonal agent is that some patients actually like IM monthly as opposed to daily oral therapy. If you asked most oncologists, they would say, "Patients prefer an oral treatment." However, there is a substantial minority that would prefer to get a shot every month.

DR LOVE: Dr Grabelsky, have you seen patients who feel a parenteral treatment is better or stronger than a pill?

DR GRABELSKY: Yes. I've had several patients express that they felt the injection was somehow stronger and that it was going to be more effective. Patients choose fulvestrant over an oral aromatase inhibitor for several reasons, including a desire to not have to worry about forgetting their medicine.

DR LOVE: One of the clinical trial concepts being evaluated is combining an aromatase inhibitor with fulvestrant. I recently interviewed John Robertson, who has done a lot of the sentinel research in this area, and I didn't realize there is this competitive inhibition between fulvestrant and estrogen that makes it rational to use an aromatase inhibitor and fulvestrant together. Richard, what are your thoughts on that?

DR ELLEDGE: Combining these nontoxic

agents that impinge on growth factor pathways is an exciting therapeutic opportunity for the future. By using single agents, I think we may have wrung just about everything we can out of the estrogen receptor. When we start combining these agents and destroying the receptor and inhibiting communication between other growth pathways, it is very exciting.

DR LOVE: Richard, at the NSABP meeting in June 2003 we were talking about a trial evaluating anastrozole, fulvestrant and gefitinib together. What is the biologic rationale for evaluating a drug like gefitinib in combination with hormonal therapy, and what is the status of that study?

DR ELLEDGE: To make a long story short, we are preparing to open that study at a couple of sites as a neoadjuvant option for older patients. Biologically, the cell has a lot of interconnecting molecular pathways that communicate with each other. Many of these are redundant and reinforce the others. Thus, if you can knock out several pathways at once, you have a better chance of potentially getting a therapeutic response as opposed to simply targeting one pathway.

Trial 25: Fulvestrant versus Tamoxifen in Postmenopausal Patients with Advanced Breast Cancer

Objective Tumor Response to Treatment in patients with ER- and/or PR-positive Tumors

	Fulvestrant (n=247)	Tamoxifen (n=212)	*p*-value
Complete response	8.9%	5.7%	
Partial response	24.3%	25.5%	
Stable disease ≥ 24 wks	23.9%	31.6%	
Objective response rate*	33.2%	31.1%	0.64
Clinical benefit rate**	57.1%	62.7%	0.22

*Complete response + partial response
**Complete response + partial response + stable disease ≥ 24 weeks

SOURCE: Howell A et al. *J Clin Oncol* 2004;22(9):1605-13. **Abstract**

Select publications

Franco S et al. **Fulvestrant (Faslodex®) demonstrates clinical benefit in heavily pretreated postmenopausal women with advanced breast cancer: a single-center experience.** *Breast Cancer Res Treat* 2003;**Abstract 439**.

Howell A et al. **Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial.** *J Clin Oncol* 2004;22(9):1605-13. **Abstract**

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To what extent does this issue of *MTP* address the following global learning objectives?

- Develop and explain a management strategy for treatment of ER-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of aromatase inhibitors in the adjuvant setting and of sequencing aromatase inhibitors after tamoxifen. . . . . 5 4 3 2 1 N/A
- Describe a strategy for sequencing hormonal therapies in the metastatic setting for patients with ER-positive metastatic disease. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the treatment of noninvasive (DCIS) and invasive breast cancer. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Richard M Elledge, MD	5 4 3 2 1	5 4 3 2 1
Kevin R Fox, MD	5 4 3 2 1	5 4 3 2 1
Gershon Locker, MD, FACP	5 4 3 2 1	5 4 3 2 1
Peter M Ravdin, MD, PhD	5 4 3 2 1	5 4 3 2 1

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