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Breast Cancer™ UPDATE

An Audio Review Journal for Oncology Nurses

Management of Estrogen Receptor-Positive Breast Cancer in the Adjuvant and Metastatic Settings

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And comments by four women with breast cancer

CE for registered nurses

Table of Contents

Breast Cancer Update for Oncology Nurses

A Continuing Education (CE) Audio Series Activity

HOW TO USE THIS MONOGRAPH

This CE activity contains both audio and print components. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program.

BreastCancerUpdate.com/Nurses includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**. There are no fees for parti-cipating and receiving CE credit for this activity. To receive credit during the period March 2004 through March 2005, participants should read the learning objectives and faculty disclosures, listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on the website at **BreastCancerUpdate.com**, and mail or fax the evaluation form with answer key to the Postgraduate Institute for Medicine.

STATEMENT OF NEED/TARGET AUDIENCE

Medical oncology, and breast cancer in particular, is one of the most rapidly advancing and developing fields of medicine. The constant emergence of new systemic agents, new indications for existing systemic agents, novel therapies, clinical trials and research findings demands that oncology nurses remain dedicated to continuing education in order to offer their patients the best care possible. This program provides nurses access to the most up-to-date research developments in breast cancer and the opinions of oncology nurses and research leaders with experience and expertise in the field. This information can be effectively translated into everyday patient management decisions.

GOAL STATEMENT

To present the most current research developments in breast cancer and to provide the perspectives of medical oncologists, oncology nurses and patients on the diagnosis and treatment of breast cancer.

EDUCATIONAL OBJECTIVES FOR THIS ISSUE OF *BREAST CANCER UPDATE* FOR ONCOLOGY NURSES

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

- Describe the mechanisms of action for hormonal therapies utilized in the treatment of estrogen receptor-positive breast cancer.
- Discuss the basis for selection and sequence of hormonal therapies in the metastatic and adjuvant settings.
- Describe fulvestrant therapy, including administration, side effects and nursing indications.
- Discuss the results of the ATAC trial and its implications in the treatment of postmenopausal women with ER-positive breast cancer.

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OTHER SPEAKERS IN THIS PROGRAM

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Stephen E Jones, MD
V Craig Jordan, PhD, DSc
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Editor's Note

First Communion

Fifty year old Mrs M has always relied on gut instinct when making major life decisions. In 1997, she sought medical care because of a difficult to describe sensation of "just not feeling well." A CAT scan revealed multiple hepatic lesions compatible with metastases from a breast cancer previously treated with adjuvant chemotherapy, tamoxifen and ovarian ablation.

Not someone to make snap decisions, Mrs M sought several opinions before embarking on a treatment course. The first medical oncologist recommended high-dose chemotherapy and bone marrow transplantation. The second medical oncologist, Dr Charles Vogel, raised the possibility of participating in a clinical trial evaluating a new and unproven but nontoxic treatment utilizing an antibody to a growth factor on the tumor cell surface.

Mrs M's inner voice told her to trust Dr Vogel, and almost seven years later, she feels totally well in continued partial remission receiving trastuzumab (Herceptin®) and anastrozole (Arimidex®).

In the midst of this frightening moment seven years ago, Mrs M learned that she would become a grandmother, and fearing that she might not be alive for her granddaughter's First Communion, she purchased a rosary to be given to the child in 2004.

"The Communion is this coming May and I'm going be there," she told me recently with quiet resolve. "I'm going to cry my eyes out, but I'll be there!" Most oncology health care professionals are frustrated that they can't do more for their patients, but rays of hope like Mrs M walk into our offices every day, teaching us valuable lessons about science, courage, love and commitment.

The *Breast Cancer Update* audio series has always emphasized the application of clinical research data into oncology practice. As a medical oncologist, my expertise is not in oncology nursing. However, after 16 years of recording educational audio interviews with physicians, nurses and patients, I have learned a bit about bridging the communication gap that sometimes exists between these key constituents in the cancer crucible.

In addition to providing the perspectives of oncology nurses, this series is designed to present the viewpoints of medical oncologists — from both community-based and research settings — and also give patients a forum in which to be heard. This current issue focuses on the management of estrogen receptor-positive breast cancer and the endocrine interventions that form the foundation of care for patients with these tumors.

The mantra of contemporary oncologic research is "targeted therapy," which has the potential to be less toxic and more effective than what sometimes seems like the

"sledgehammer" approach of chemotherapy. Anastrozole, other endocrine therapy and trastuzumab are perhaps the most cutting-edge targeted breast cancer treatments. All you have to do is look at Mrs M to see the power of these therapies. From her appearance, one would never guess that she was ill — let alone with a condition few patients survive long term.

The clinical courses of the other three women interviewed for this program exemplify the spectrum of endocrine interventions observed in clinical practice. Mrs S, a 67-year-old retired schoolteacher, is currently in the process of receiving five (or more) years of adjuvant anastrozole. This strategy has only been widely embraced in the two years since Dr Michael Baum presented the first results of the massive ATAC trial suggesting that anastrozole might be a better adjuvant choice than tamoxifen for postmenopausal women.

This program includes comments from Dr Baum and Dr Gabriel Hortobagyi, both of whom chronicle the evolution of this exciting therapy. Oncology nurses perhaps have less exposure than oncologists to the ins and outs of sifting through emerging research information like the ATAC trial. However, it is essential that all parties on the interdisciplinary team understand each other's roles. Hopefully, our program will provide nurses more insight into the thought processes of the oncologists they work with and the way these individuals approach treatment recommendations.

Eighty-year-old Mrs T is another example of the rapid emergence of targeted therapy for breast cancer. She has received two aromatase inhibitors for metastases in multiple bones, and another very high-tech therapy, fulvestrant (Faslodex®) — the first commercially available "estrogen receptor downregulator." Like the aromatase inhibitors, this treatment is remarkably nontoxic, although it must be administered monthly via intramuscular injection.

Fulvestrant has antitumor activity that is comparable and perhaps superior to our best endocrine treatments for postmenopausal women (aromatase inhibitors) and also has the unique mechanism of action of obliterating the estrogen receptor, which holds the promise of new potentially more effective treatment strategies. Drs Stephen Jones and Robert Carlson have had key roles in the evolution of this research approach, and in this issue they comment on where this treatment approach is likely to lead.

The other woman interviewed for this issue is Mrs B, an 83-year-old former nurse who has been battling breast cancer for 22 years. After nine years of treatment for metastases she is struggling to maintain a reasonable quality of life. Gasping between breaths during our conversation, she also demonstrated a very refreshing sense of humor. When I asked about her concerns for the future, she quipped, "You mean, am I afraid of dying? Well, no…maybe I'll go to a better place…a place where I can breathe!"

Mrs B's oncologist, Dr Sandra Franco, and her oncology nurse, Ms Cynthia Frankel, have obvious enthusiasm for clinical research that will create more miracles like Mrs M attending her granddaughter's upcoming First Communion. But oncology professionals also know that while the clock may run out on science, there is always a critical role for caring and compassion in confronting what can be, at times, a relentless disease.

—Neil Love, MD

Patient Case Summaries

Mrs S: A 67-Year-Old Retired Schoolteacher Receiving Adjuvant Treatment

Clinical Issues:

- Chemotherapy-related side effects compared to endocrine therapy
- Research background for selection of adjuvant hormonal therapy for postmenopausal women with ER-positive tumors
- Differences between side-effect profiles of anastrozole and tamoxifen

Mrs S was diagnosed with ER-positive breast cancer three years ago. Although presented with the option of lumpectomy, Mrs S decided to undergo mastectomy. An axillary node dissection revealed one positive lymph node. Following her primary therapy, Mrs S elected six cycles of adjuvant CEF (in lieu of a doxorubicin-containing regimen) to potentially decrease the likelihood of toxicity. Despite this decision, she experienced alopecia, constant nausea, weight gain and profound fatigue. At the completion of adjuvant chemotherapy, Mrs S began hormonal therapy with anastrozole and continues to receive this treatment with minimal side effects other than arthralgias relieved by nonsteroidal anti-inflammatory drugs.

Patient Perspective: Mrs S

"Chemotherapy was not pleasant. It was a very traumatic experience and the side effects were not good. Besides the hair loss, which was horrible, I was constantly nauseous, had headaches and was tired all of the time. I'm the type of person who can take on any problem, but when I was on chemotherapy my mind was willing but my body just wasn't able. I had no energy and I didn't care about anything. All I did was sleep. After chemotherapy, Dr Franco wanted me to start hormonal therapy. She explained to me the pros and cons, and based on what she told me, anastrozole seemed like a more viable choice than tamoxifen.

Unfortunately, people in my family have been on tamoxifen and ended up having hysterectomies, blood clots and all sorts of problems, so I felt anastrozole was a safer choice for me. I have experienced some joint pain with anastrozole. It started a couple of months after I started taking the drug. Some days it's better and some days it is worse. I think it depends on the weather. Usually, I just take ibuprofen or something like that and then it's okay."

Mrs T: An 80-Year-Old Widow with Metastatic Disease

Mrs T was diagnosed with breast cancer at the age of 69. At that time she was working part-time and caring for her husband who was being treated for Parkinson's disease. During her initial course of therapy, Mrs T underwent mastectomy, axillary dissection, radiation therapy, 6 cycles of adjuvant CAF chemotherapy and then received tamoxifen. She remained cancer-

free for four years until a routine pelvic x-ray following an automobile accident revealed bony metastases in the hip. Mrs T was treated with pelvic irradiation and was started on anastrozole and pamidronate. The pain subsided and she remained on anastrozole for more than three years. At that time, a follow-up MRI conducted because of back pain revealed metastases in the lumbar spine. Anastrozole was discontinued, and monthly intramuscular injections of fulvestrant were initiated. The patient experienced relief of the back pain and remained asymptomatic and fully functional on fulvestrant for two years. In late 2003, another MRI following complaints of further pain in the upper back revealed a new metastasis in her thoracic spine. Two months later her treatment was switched from fulvestrant to the aromatase inhibitor exemestane, which has ameliorated her back pain.

Clinical Issues:

- Sequencing of hormonal therapies after progression on tamoxifen
- Role of chemotherapy in the elderly patient with ER-positive metastatic disease
- Quality of life for patients on hormonal therapy for metastatic disease
- Patient compliance with oral endocrine treatments

Patient Perspective: Mrs T

"I had been receiving anastrozole for about three or four years without any problems when I began to have pains in my back similar to the original pain I had in my hip. Dr Vogel ordered the necessary tests, which showed that the disease was getting worse. Based on these findings, he felt that the anastrozole had stopped working so he put me on fulvestrant. I received two fulvestrant injections every month, one on each side. They were simple. I've never been a pill taker, and with the injection, I didn't have to worry about taking a pill every day. I didn't mind the injection at all. I really didn't have any discomfort or side effects from the medication either, and it wasn't too long — maybe just a couple of months — before the pain in my back started getting better."

Mrs M: A 50-Year-Old Grandmother with HER2-Positive Hepatic Metastases

In 1994, at the age of 40, Mrs M was diagnosed with ER-positive, HER2-positive breast cancer. She was premenopausal and received adjuvant chemotherapy, tamoxifen and ovarian ablation. In 1997, Mrs M began to feel ill and she returned to her oncologist. Multiple metastases were discovered in her liver. Because her tumor overexpressed HER2, Mrs M's oncologist recommended enrollment in a clinical trial testing the efficacy of the anti-HER2 antibody, trastuzumab, as a single agent. Trastuzumab was given weekly and she experienced no side effects. The hepatic lesions

Clinical Issues:

- Algorithm for the treatment of ER-positive, HER2-positive breast cancer
- Use of trastuzumab in combination with hormonal therapy
- Continuation of trastuzumab after progression
- Importance of enrolling patients in clinical trials

decreased in size and the patient felt well again. After three years, the liver metastases progressed and anastrozole was added to the trastuzumab, resulting in another response. Mrs M continues to receive her trastuzumab infusions every week and takes her anastrozole daily. She has been essentially without symptoms, living with metastatic disease for eight years.

Patient Perspective: Mrs M

"When I found out my cancer had come back, Dr Vogel sat down with me and discussed the different treatment options. He told me about chemotherapy and also about a clinical trial he was running with trastuzumab. I had heard a lot about chemotherapy and was aware that it would make me feel sick. I am the type of person who likes to knock on different doors and not necessarily go through the last door first. I would rather start with the first door. In this case, starting with trastuzumab and avoiding chemotherapy was the door I thought I should go for first."

Mrs B: An 83-Year-Old Retired Nurse with a 22-Year History of Breast Cancer and Nine Years of Treatment for Metastatic Disease

Mrs B was first diagnosed with breast cancer 22 years ago. For the past nine years, she has had metastatic disease. She has received multiple hormonal therapies, including anastrozole and fulvestrant, with good response. Like many women with ER-positive breast cancer, endocrine therapy finally lost its effectiveness, and Mrs B subsequently received a number of chemotherapeutic agents. Currently, she has highly symptomatic pulmonary metastases, which is significantly interfering with her lifestyle.

Clinical Issues:

- Long-term survival with ER-positive breast cancer
- Salvage therapies for ER-positive metastatic breast cancer
- Chemotherapeutic options for the symptomatic elderly patient
- Counseling patients on end-of-life issues

Patient Perspective: Mrs B

"When I sit in the treatment room I often listen to the conversations of other patients and sometimes I just want to tell them that we are in this for the long haul. I am in my twenty-second year, and these women will have better chances than I had because of all of the research and innovation that has gone on. There will be drugs available to them that were not available to me. I really did not expect to live this long. I feel lucky, I really do."

Excerpts from the Audio Program:

Determining the Risk of Recurrence and Impact of Adjuvant Systemic Therapy

We evaluate tumor size, grade, node status and whether hormone receptors and HER-2 receptors are present. With all of those characteristics, we estimate prognosis and the risk for recurrence. Based on extensive data from many clinical trials, we can also determine the potential benefit of a number of possible adjuvant treatments and whether the patient might be eligible for a clinical trial.

Often, I have a patient with an excellent prognosis after local therapy and endocrine treatment and the additional benefit that patient will derive from chemotherapy might be as low as one percent. In that case, the patient has to decide whether the risks and toxicities of going through chemotherapy are really worth the one percent extra benefit. I don't think that is for me to decide; it's for the patient to decide. My role as a physician is to inform the patient and give her the tools she needs to make the right decision. It amazes me how often these women will choose to receive chemotherapy for such a small benefit.

— Sandra Franco, MD

Breast cancer patients don't ever want to look back and say, "I should have been treated. Did I lose a chance to be cured by not moving forward with a therapy that's been recommended?" In the adjuvant setting, women often have a very difficult time with the decision. The most important message we provide to these women is, "In the adjuvant setting, this is our opportunity to cure your disease. And once we are beyond this setting and dealing with metastases, we can certainly control your disease and you can live with good quality of life if things go well, but if we don't take the opportunities that exist in the adjuvant setting, we don't have another opportunity." And that seems to hit home.

— Cynthia Frankel, RN

Mechanism of Action of Endocrine Therapies

Tamoxifen is a selective estrogen-receptor modulator that binds to the estrogen receptor and causes inhibition of signal transduction by blocking the receptor. The estrogen receptor is a complicated structure that has two parts. Tamoxifen will activate one part of the receptor and de-activate the other. That is why it is called a modulator.

Fulvestrant, on the other hand, will de-activate both parts of the estrogen receptor, causing full blockage of signal transduction and resulting in disappearance of the estrogen receptor.

By contrast, aromatase inhibitors work away from the cancer cell by blocking aromatase enzymes in the breast, liver and fat. Aromatase converts two androgenic hormones produced in the adrenal gland — androstenedione and DHEA — into two estrogenic hormones — estradiol and estrone. Even though levels are much lower, estrogen production continues in postmenopausal women. Thus aromatase inhibitors can be used to essentially block the conversion of androgens into estrogens.

— Sandra Franco, MD

ATAC Adjuvant Trial Results

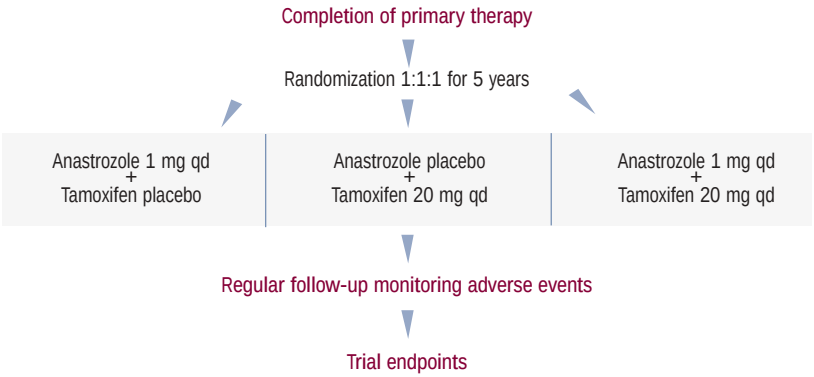
There are over 9,000 patients from all over the world in this study, with just over 3,000 patients in each arm. The headline news is that it looks as if there is something after tamoxifen — there is a significant advantage to anastrozole compared to tamoxifen. The real surprise is that the combination of anastrozole and tamoxifen looks no different than tamoxifen alone.

At this point, my preferred therapy for the postmenopausal woman with receptor-positive breast cancer is anastrozole unless contraindicated — for example, in women with high risk of osteoporosis or with osteoporosis. If a clinician is concerned about a loss of bone mineral density, it's something that could be monitored. You don't withhold chemotherapy because you're worried about white cell count — you give it but you closely monitor white cell count. Osteopenia is not a crisis like neutropenia can be, and by doing a bone mineral density at entry and then intervening with a bisphosphonate when necessary, say if bone mineral density is starting to fall, it can be managed. So the one adverse effect favoring tamoxifen over anastrozole, I think, can be managed.

— Michael Baum, ChM, FRCS

Figure 1.1

ATAC Trial Design — Postmenopausal Women with Invasive Breast Cancer



SOURCE: Buzdar A. Presentation, San Antonio Breast Cancer Symposium, 2002.

Implications of the ATAC Trial in Clinical Practice

The results of the ATAC trial are quite compelling. Even if you assume for the sake of argument that the disease-free survival curves will come together with further follow up, the safety profile of anastrozole is still clearly better than that of tamoxifen. I cannot prevent endometrial cancer short of removing the uterus, but I can prevent or treat osteoporosis and fractures.

Since the safety profile of anastrozole is better than that of tamoxifen and it is therapeutically superior, I have a problem not offering anastrozole to my postmenopausal patients — not as

a neutral choice but as a better choice. I discuss with my patients the enormous amount of clinical experience we have with tamoxifen, but if my sister were postmenopausal and developed breast cancer today, I would certainly recommend anastrozole as opposed to tamoxifen.

— Gabriel N Hortobagyi, MD

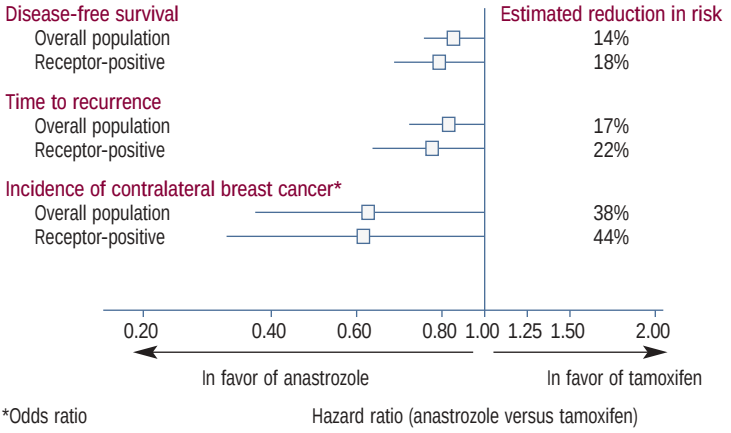
After the ATAC trial results were initially presented, I began speaking with my patients about the results. I told them that the data were still early, and we discussed the risk-benefit profile and quality-of-life issues. Then they made the decision to receive anastrozole or tamoxifen.

There are some women who are so concerned about the potential for osteoporosis with anastrozole, or who already are suffering from arthritic symptoms, that they will say, "If those side effects are predominant with anastrozole, then I'd prefer to go with tamoxifen." On the other hand, women who are deathly afraid of the uterine cancer risk and blood clots may choose to go with anastrozole. At this time, both of these are still very viable options.

— Charles L Vogel, MD, FACP

Figure 1.2

ATAC Trial: Summary I (Efficacy) — Updated Analysis



SOURCE: Buzdar A. Presentation, San Antonio Breast Cancer Symposium, 2002.

Safety Profiles in the ATAC Trial

One of the most exciting parts of the ATAC trial is the safety profile of anastrozole. There was a highly significant reduction in the incidence of hot flashes, vaginal discharge and vaginal bleeding. This reduction in vaginal bleeding is significant because it will cut down the number of women referred to gynecologists to rule out endometrial cancer.

Perhaps even more important is the significant reduction in the anastrozole arm in life-threatening events such as strokes, cerebrovascular accidents and thromboembolic events.

In terms of side effects, about 8 percent of women receiving anastrozole complain about arthralgias. There is also a numerically modest but highly significant excess fracture rate in the anastrozole arm. Apart from bone mineral density — which I think we can handle if we anticipate it — the safety profile strongly favors anastrozole over tamoxifen.

— Michael Baum, ChM, FRCS

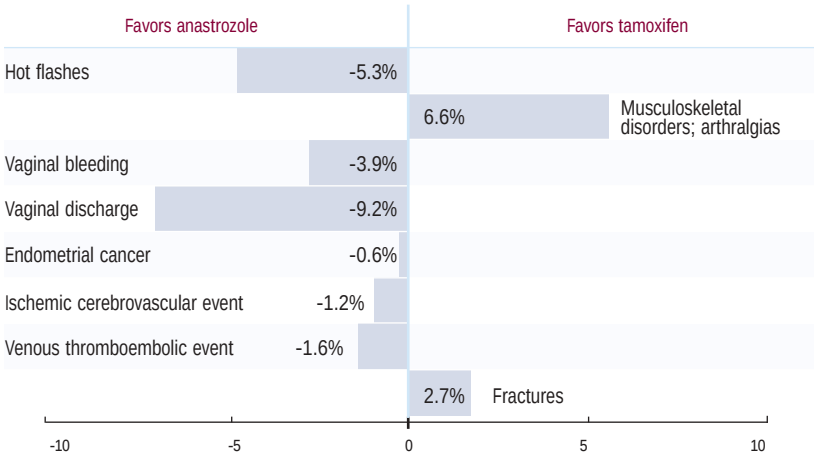
Endometrial Cancer and Tamoxifen

I think women understand that even though we use adjuvant therapies to attempt to cure their disease, there is a risk of some of them causing other cancers. I don't know what could be scarier and I think that is the reason many patients who are on tamoxifen focus on endometrial cancer even though there is just a one percent risk.

— Cynthia Frankel, RN

Figure 1.3

ATAC Trial: Significant Differences in Predefined Adverse Events Between Anastrozole and Tamoxifen



DERIVED FROM: Baum M, et al. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses.** *Cancer* 2003;98(9):1802-10. **Abstract**

Implications of Canadian and Italian Trials of Sequencing of Tamoxifen and Aromatase Inhibitors

A recently presented Italian trial has shown a significant benefit for patients switching to anastrozole following two or three years of tamoxifen. These data go along with data from a Canadian trial showing a similar result for starting an aromatase inhibitor after five years of tamoxifen. There is still a lot about this that is not known; however, I think these new data should be discussed with women who are currently being treated with tamoxifen or who have

completed five years of tamoxifen so that they can make their own decisions about switching to an aromatase inhibitor.

— Sandra Franco, MD

Providing Patients with Treatment Options and Recommendations

One of our major goals is to fully educate our patients by giving them relevant, accurate and complete information, so that they understand their prognosis, treatment options and the benefit-to-risk ratio they will face with each of those options. But we can't stop there. We also need to make a recommendation after that education. Obviously this recommendation will incorporate our biases and prejudices, but we are better qualified — even with those biases and prejudices — than a patient who just had "oncology 101" during the previous 20 to 30 minutes.

Over the past 30 years in medicine we have moved from a paternalistic approach to the other extreme. Many of my colleagues try to be so neutral that they do not make a recommendation. The burden of decision making has been removed completely from the physician, who is best qualified to make that choice or recommendation, to the patient, who sometimes is but most of the times is not in the best position to make that choice without guidance.

I understand and agree that patients need to have autonomy. We clearly have the obligation to inform them fully, but I think we need to go beyond that. We have to get to know our patients and understand their motivations, their understanding of risks and benefits, their definition of therapeutic gain and their level of acceptance of risks and side effects. As physicians, we need to help them make a decision. To abrogate that responsibility is an unfortunate — and I hope temporary — trend in the medical profession.

— Gabriel N Hortobagyi, MD

Tolerability of Fulvestrant

Injection site reactions and hot flashes are the only side effects that I've observed in patients receiving fulvestrant. There may be something about the administration technique for fulvestrant that can affect the pain that is infrequently experienced. If the injection is inadvertently given subcutaneously into fat, it's more painful than if it's given intramuscularly. It may be that many of the women who have pain with the injection are not actually receiving true intramuscular injections; this is more likely to occur in women who are obese.

— Robert W Carlson, MD

We were involved in the initial North American trial of fulvestrant versus anastrozole in women with ER-positive tumors. I personally administered many of the injections to patients in the trial and they were tolerated very well. No patient dropped out of the trial because of the injections. The bottom line with fulvestrant is that it is an oily substance and it takes a good minute to give the injection. You need to take your time.

Sometimes a little bit of seepage can cause a rash in women receiving their first injections. When we give the injections deep in the muscle, hold pressure and wipe off that area to remove the seepage, no injection reactions are noted.

— Sharon Carrasco, RN, MSN, OCN

Figure 1.4

Trials 20, 21: Fulvestrant versus Anastrozole Tolerability in Tamoxifen-Treated Patients with Advanced Disease

	Number of adverse events (%)		
	Fulvestrant n=423	Anastrozole n=423	*p*-value
Hot flashes	89 (21.0)	87 (20.6)	0.91
Gastrointestinal disturbances	196 (46.37)	185 (43.7)	0.53
Weight gain	4 (0.9)	7 (1.7)	0.35
Vaginitis	11 (2.6)	8 (1.9)	0.51
Thromboembolic disease	15 (3.5)	17 (4.0)	0.68
Joint disorders	23 (5.4)	45 (10.6)	0.004
Urinary tract infection	31 (7.3)	18 (4.3)	0.06
Withdrawn due to adverse events	12 (2.8)	8 (1.9)	—

SOURCE: Robertson J et al. *Cancer* 2003;98:229-30.

Sequencing Hormonal Agents in Postmenopausal Women

In a postmenopausal woman whose disease relapses on adjuvant tamoxifen, I would use fulvestrant because I've seen some very long remissions with it. I will use an aromatase inhibitor later because data indicate that patients with disease that progresses on fulvestrant can still respond to other endocrine treatments (e.g., aromatase inhibitors and megestrol acetate).

A couple of reports have evaluated the response to fulvestrant in patients who have received an aromatase inhibitor. A fairly small Swiss study reported that about one-third of patients derived clinical benefit from fulvestrant after treatment with tamoxifen or an aromatase inhibitor. A compassionate-use study reported at ASCO 2003 reported about 60 patients with fulvestrant as second-, third- or fourth-line therapy. Fulvestrant had a more than 50 percent clinical benefit rate in those patients.

— Stephen E Jones, MD

Women with breast cancer who fail on tamoxifen can clearly respond to fulvestrant, and the rate of response is equivalent to that seen with anastrozole. Also, in women with disease that has failed anastrozole who are then crossed over to fulvestrant, the rate of clinical benefit is substantial and in the range of approximately 40 percent. Patients who are crossed over from fulvestrant to aromatase inhibitors also show response rates of approximately 40 percent.

Surprisingly, the magnitude of benefit from fulvestrant does not predict whether the cancer will respond to a subsequent hormonal maneuver. One rule of thumb in the past has been that the magnitude and duration of response to the most recent hormonal therapy predicts for the likelihood of response for subsequent hormonal therapies. A small retrospective study suggests that may not be the case with fulvestrant.

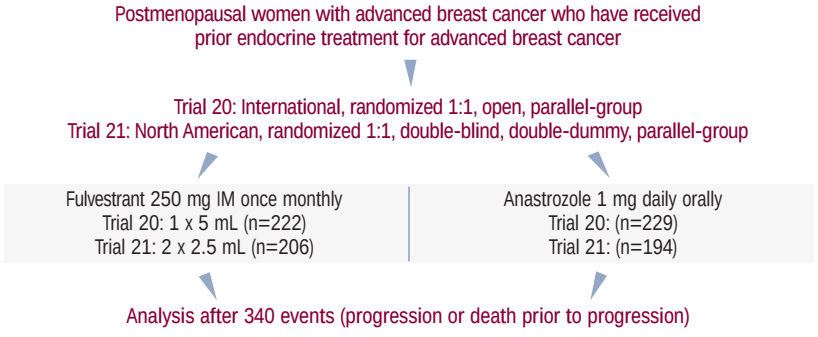
— Robert W Carlson, MD

We know that fulvestrant is at least as efficacious as the aromatase inhibitors, but I really don't know where I would sequence it because the aromatase inhibitors are pills. I think fulvestrant is and will continue to be most useful for patients on fixed incomes who can't afford the aromatase inhibitors or those for whom there are concerns about their reliability in taking oral medications. Women in those situations can be treated quite nicely with fulvestrant, and we have data indicating that it is probably at least equivalent.

— Charles L Vogel, MD, FACP

Figure 1.5

Trials 20 and 21: Fulvestrant versus Anastrozole



SOURCES: Howell A et al. *J Clin Oncol* 2002;20:3396-403. Mauriac L et al. *Eur J Cancer* 2003;39(9):1228-33. Osborne CK et al. *J Clin Oncol* 2002;20:3386-95.

Fulvestrant's Mechanism of Action

Fulvestrant binds with the estrogen receptor monomer in the cytoplasm and prevents the dimerization of the estrogen receptor, which is required for exertion of its maximal activity. Lack of estrogen receptor dimerization results in accelerated degradation of the ER-fulvestrant complex. Ultimately, there is a loss of estrogen receptors within the cells.

The estrogen receptor is continually regenerated, so continued exposure to fulvestrant is required. After fulvestrant is discontinued, the estrogen receptor will, with time, reappear in cells. The fact that we see subsequent hormonal responses is convincing biological or clinical evidence that the estrogen receptors do reappear.

— Robert W Carlson, MD

Compliance with Oral Therapy

Compliance is definitely an overlooked problem. You would think that a woman with symptomatic metastatic disease who is participating in a clinical trial would be constantly reminded of her disease enough to take her treatment, but I have had patients come in and say, "I forgot to take my study drug." Now think about someone with very stable metastatic disease that comes in every month or every three months. There is no doubt in my mind that compliance is an issue.

— Sandra Franco, MD

There is a commercial that says "it's not hard to remember, it's just easy to forget," and I think women like the fact that they can come in, receive their therapy and not have to worry about taking their medication every day. I think fulvestrant probably increases compliance and decreases anxiety.

When I first started working with women with breast cancer, most of them sort of gave up their lives and spent the rest of their time just getting their ducks in order. With breast cancer today, women are raising families, working and making their place in society. Many of them can barely make time for their treatments, so I think compliance is definitely an issue.

—Cynthia Frankel, RN

Figure 1.6

Fulvestrant versus Anastrozole: Efficacy Data

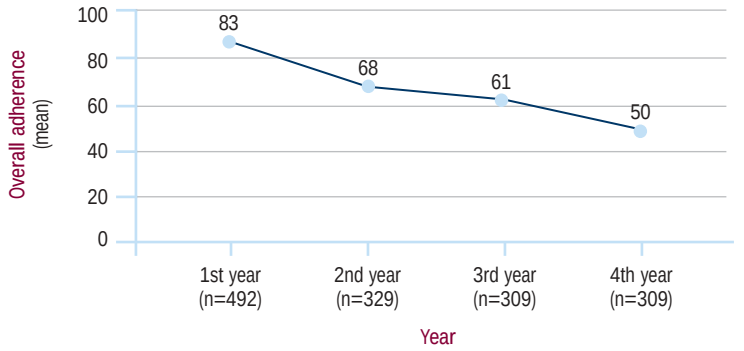
	Trial 0020[1]		Trial 0021[2]		Combined analyses[3,4]	
	Fulvestrant n=222	Anastrozole n=229	Fulvestrant n=206	Anastrozole n=194	Fulvestrant n=428	Anastrozole n=423
Median time to progression	5.5 mo	5.1 mo	5.4 mo	3.4 mo	5.4 mo	4.1 mo
Clinical benefit*	44.6%	45.0%	42.2%	36.1%	43.5%	40.9%
Median duration of response	15 mo	14.5 mo	19.0 mo	10.8 mo	16.7 mo	13.6 mo

*Clinical benefit (CR + PR + SD ≥ 24 weeks)

SOURCES: Robertson J et al. *Cancer* 2003;98:229-30.[1]Howell A et al. *J Clin Oncol* 2002;20:3396-403. [2]Osborne CK et al. *J Clin Oncol* 2002;20:3386-95. [3]Mauriac L et al. *Eur J Cancer* 2003;39(9):1228-33. [4]Parker LM et al. *Proc ASCO* 2002;**Abstract 160**.

Figure 1.7

Long-Term Adherence to Adjuvant Tamoxifen Therapy in Eligible Patients from 1991 Index Year Cohort



SOURCE: Partridge A et al. **Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer.** *J Clin Oncol* 2003;21(4):602-6. **Abstract**

SELECT PUBLICATIONS:

The ATAC Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *Lancet* 2002;359:2131-9. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Tamoxifen for early breast cancer: An overview of the randomised trials.** *Lancet* 1998;351:1451-67. **Abstract**

Baum M et al. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses.** *Cancer* 2003;98(9):1802-10. **Abstract**

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;**Abstract 3**.

Bundred N, Howell A. **Fulvestrant (Faslodex): Current status in the therapy of breast cancer.** *Expert Rev Anticancer Ther* 2002;2(2):151-60. **Abstract**

Carlson RW. **Sequencing of endocrine therapies in breast cancer — integration of recent data.** *Breast Cancer Res Treat* 2002;75(Suppl 1):27-32; discussion 33-5.

Dow KH. **Existing and emerging endocrine therapies for breast cancer.** *Cancer Nurs* 2002;25(Suppl 2):6-11. **Abstract**

Goss PE et al. **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1793-802. **Abstract**

Hancock CM. **Fulvestrant antiestrogen for treatment of breast cancer.** *Clin J Oncol Nurs* 2003;7(2):201-2. **Abstract**

Howell A et al. **Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment.** *J Clin Oncol* 2002;20:3396-403. **Abstract**

Lynn J. **The oncology nurse's role in educating patients on endocrine therapy for metastatic breast cancer — focus on fulvestrant.** *Cancer Nurs* 2002;25(Suppl 2):12-7. **Abstract**

Lynn J. **Estrogen receptor downregulators: New advances in managing advanced breast cancer.** *Cancer Nurs* 2002;25(Suppl 2):2-5; quiz 18-9. **Abstract**

Osborne CK et al. **Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial.** *J Clin Oncol* 2002;20:3386-95. **Abstract**

Palmieri FM, Perez EA. **Recent advances in adjuvant therapy for breast cancer.** *Semin Oncol Nurs* 2003;19(4 Suppl 2):10-6. **Abstract**

Parker LM. **Sequencing of hormonal therapy in postmenopausal women with metastatic breast cancer.** *Clin Ther* 2002;24(Suppl C):43-57. **Abstract**

Partridge AH et al. **Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer.** *J Clin Oncol* 2003;21(4):602-6. **Abstract**

Winer EP et al. **American Society of Clinical Oncology Technology Assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor positive breast cancer: Status report 2002.** *J Clin Oncol* 2002;20(15):3317-27. **Abstract**

Winer EP et al. **American Society of Clinical Oncology technology assessment working group update: Use of aromatase inhibitors in the adjuvant setting.** *J Clin Oncol* 2003;21(13):2597-9. No abstract available

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The European and North American trials of fulvestrant versus anastrozole in postmenopausal patients with metastatic disease demonstrated:
   a. Equivalent survival
   b. Longer duration of response favoring fulvestrant
   c. Superior time to progression and response rate favoring anastrozole
   d. Both a and b

2. Fulvestrant can be administered intramuscularly either as one 5-cc injection or two 2.5-cc injections.
   a. True
   b. False

3. Which of the following is a recognized side effect of fulvestrant?
   a. Nausea and vomiting
   b. Hair loss
   c. Neutropenia
   d. None of the above

4. Fulvestrant is an estrogen receptor upregulator.
   a. True
   b. False

5. Fulvestrant is useful in women with both estrogen receptor-positive and estrogen receptor-negative breast cancers.
   a. True
   b. False

6. **In the adjuvant and metastatic settings, side effects are less in patients treated with hormonal therapy versus cytotoxic chemotherapy.**
   a. True
   b. False

7. Aromatase inhibitors have been well studied only in postmenopausal women and should not be used in premenopausal patients.
   a. True
   b. False

8. Which of the following toxicities are associated with anastrozole:
   a. Endometrial cancer
   b. Thromboembolic events
   c. Osteoporosis
   d. All of the above

9. The safety profile from the ATAC trial shows a significant reduction in hot flashes and vaginal bleeding in patients on anastrozole compared to those on tamoxifen.
   a. True
   b. False

10. Which of the following was not an arm of the ATAC adjuvant trial in postmenopausal women with early breast cancer?
   a. Toremifene
   b. Tamoxifen
   c. Anastrozole
   d. Combination of tamoxifen and anastrozole

11. The efficacy data from the 47-month follow-up of the ATAC trial favors which arm of the study?
   a. Anastrozole
   b. Tamoxifen
   c. Anastrozole/tamoxifen combination
   d. The efficacy data is equivalent in all three arms

12. LHRH agonists used in premenopausal women produce a chemical oophorectomy that is not reversible.
   a. True
   b. False

13. After menopause, estrogen is no longer produced by the ovary and the estrogen levels in the body fall to zero.
   a. True
   b. False

14. Which of the following mechanisms of hormonal therapy are utilized in patients with ER-positive breast cancer?
   a. Selective estrogen receptor modulators
   b. Estrogen receptor downregulators
   c. Aromatase inhibitors
   d. LHRH agonists
   e. All of the above

Post-test Answer Key: 1d, 2a, 3d, 4b, 5b, 6a, 7a, 8c, 9a, 10a, 11a, 12b, 13b, 14e

Evaluation Form:
Breast Cancer Update for Oncology Nurses — Issue 1, 2004

PROJECT ID:
04-2041-ES-12

Postgraduate Institute for Medicine (PIM) respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgement of participation for this activity.

Please answer the following questions by circling the appropriate rating:
5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor

EXTENT TO WHICH PROGRAM ACTIVITIES MET THE IDENTIFIED GOAL

- To present the most current research developments in breast cancer and to provide the perspectives of medical oncologists, oncology nurses and patients on the diagnosis and treatment of breast cancer. 5 4 3 2 1

EXTENT TO WHICH PROGRAM ACTIVITIES MET THE IDENTIFIED OBJECTIVES

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

- Describe the mechanism of action for hormonal therapies utilized in the treatment of estrogen receptor-positive breast cancer. 5 4 3 2 1
- Discuss the basis for selection and sequence of hormonal therapies in the Metastatic and adjuvant settings. 5 4 3 2 1
- Describe fulvestrant therapy, including administration, side effects and nursing indications. 5 4 3 2 1
- Discuss the results of the ATAC trial and its implications in the Treatment of postmenopausal women with ER-positive breast cancer. 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Sandra S Franco, MD	5 4 3 2 1	5 4 3 2 1
Cynthia Frankel, RN, OCN	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Was timely and will influence how I practice 5 4 3 2 1
Will assist me in improving patient care 5 4 3 2 1
Fulfilled my educational needs 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

IMPACT OF THE ACTIVITY

The information presented (check all that apply):

- ☐ Reinforced my current practice/treatment habits.
- ☐ Provided new ideas or information I expect to use.
- ☐ Will improve my practice/patient outcomes.
- ☐ Enhanced my current knowledge base.

Will the information presented cause you to make any changes in your practice?

☐ Yes ☐ No

If yes, please describe any change(s) you plan to make in your practice as a result of this conference:

. . . . . .

. . . . . .

IMPACT OF THE ACTIVITY (continued)

How committed are you to making these changes?

(5 = very committed; 1 = not at all committed) 5 4 3 2 1

FUTURE ACTIVITIES

Do you feel future activities on this subject matter are necessary and/or important to your practice?

☐ Yes ☐ No

Please list any other topics that would be of interest to you for future educational activities:

.....

.....

FOLLOW-UP

As part of our ongoing continuous quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey.

☐ No, I'm not interested in participating in a follow-up survey.

Additional comments about this activity:

.....

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REQUEST FOR CREDIT

Name ..... Degree .....

Organization ..... Specialty .....

Address .....

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I certify my actual time spent to complete this educational activity to be:

☐ I participated in the entire activity and claim 3.9 contact hours.

☐ I participated in only part of the activity and claim _____ contact hours.

Signature ..... Date .....

If you wish to receive acknowledgement of participation for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation and FAX to: (303) 790-4876 or mail to Postgraduate Institute for Medicine, 367 Inverness Parkway, Suite 225, Englewood, CO 80112.

Breast Cancer™ UPDATE

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