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Breast Cancer™ UPDATE

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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2 audio tapes

2 audio CDs

Print supplement

CME Certified

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Breast Cancer Update: A CME Audio Series and Activity

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.

To bridge the gap between research and patient care, Breast Cancer Update utilizes one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists medical oncologists in the formulation of up-to-date clinical management strategies.

Issue 4, 2002 of Breast Cancer Update consists of discussions with four oncology research leaders on a variety of important issues, including the results of the ATAC trial, the estrogen receptor downregulator fulvestrant, the treatment of the HER2-positive patient (including use of trastuzumab), the use of capecitabine for metastatic breast cancer and the current neoadjuvant clinical trials of taxane-based chemotherapy.

Educational objectives

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

- Describe the clinical implications of the ATAC trial results
- Review the side-effect profiles of anastrozole and tamoxifen
- Discuss the biology and mechanism of action of fulvestrant
- Discuss the role of capecitabine in the treatment of metastatic disease
- Review the design and rationale for the current MD Anderson neoadjuvant/adjuvant trial of paclitaxel versus docetaxel-capecitabine
- Describe potential strategies for treating the HER2-positive patient
- Review the preliminary results of the Phase II trial examining the combination of trastuzumab/carboplatin/paclitaxel

Accreditation statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Postgraduate Institute for Medicine and NL Communications, Inc.

The Postgraduate Institute for Medicine is accredited by the ACCME to provide continuing medical education for physicians and takes responsibility for the content, quality and scientific integrity of this CME activity.

Designation statement

The Postgraduate Institute for Medicine designates this educational activity for a maximum of 3 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

Faculty disclosure statements

The Postgraduate Institute for Medicine has a conflict of interest policy that requires course faculty to disclose any real or apparent commercial financial affiliations related to the content of their presentations/materials. It is not assumed that these financial interests or affiliations will have an adverse impact on faculty presentations; they are simply noted in this supplement to fully inform participants.

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How to use this supplement

This monograph supplements the audio program and contains edited comments, clinical trial schemas, graphics and references. **BreastCancerUpdate.com** includes a full transcription of the audio program and an easy-to-use representation of each page of this booklet, allowing users to link immediately to relevant full-text articles, abstracts, trial information and other web resources indicated throughout this guide in **red underlined text.** This regularly updated web site also features an extensive breast cancer bibliography, clinical trial links, a "breast cancer web tour" and an audio library with excerpts from interviews and meetings catalogued by topic.

Editor's Note

"Doctor, what would you do if you were in this situation?"

Do you think most oncologists recommend treatments to patients with metastatic breast cancer that they would want to have in the same situation?

"At some level I hope they do, but on another level, I hope they don't. Let me explain: When we choose between similar treatments with different side effects, what we should recommend to our patients is not necessarily what we would choose for ourselves, but the treatment which — after talking to that patient — fits best with that patient's preferences. Often the treatment recommendation may not be the one we would choose for ourselves. For example, I might be terrified of neurotoxicity, but my patient may not. Maybe, playing the piano is everything to me. But, more often than not, we do recommend the treatment that we would choose for ourselves, and patients go along with it since there is not that much variability in people's preferences."

— Eric P Winer, MD

Nothing is more fascinating than "picking the brain" of a thoughtful and experienced research leader like Eric Winer. Reflecting on his comments in the enclosed audio program, I realize that one of the greatest challenges that we face in oncology is gaining enough emotional proximity to the patient to provide empathetic care, while simultaneously distancing ourselves adequately to allow for rational management of the case.

To assist medical oncologists in negotiating the slender divide separating them from their patients in choosing less than perfect therapies, the Breast Cancer Update series queries research leaders about how they integrate emerging trial data into clinical decision-making. My role, in interviewing these investigators, is to pose tough and sometimes unanswerable questions about patient care in order to arrive at clinical examples that physicians can utilize in practice. But these theoretical conversations often do not address the very real emotions felt by cancer patients and loved ones.

"I was so afraid — and I'm the type of person who usually has an answer for everything and can control everything — but all of a sudden, I felt out of control. I would have loved to be able to say, 'Well, yes, doctor. Let's sit down and discuss the plan. Let's do this. Let's do that.' I felt totally lost, and the only thing I could think was to ask him, "If this were your wife, what would you do? What would you recommend?"

— 44-year-old woman with breast cancer reflecting on the initial diagnosis.
(Miami Breast Cancer Conference patient video presentation)

The question this woman asks is so poignant that it compels us to wonder: What if this truly was the case? What if you or your loved one was suddenly in a similar situation? What choices would you make? What factors would influence your decision? Here is an interesting exercise in that regard:

Imagine that you were in the following situation:

Three years ago, you were diagnosed with a localized cancer that was excised. Based on a long-term predicted risk to develop metastases of about 50%, you were treated for six months with adjuvant combination chemotherapy that resulted in alopecia, fatigue and moderate gastrointestinal toxicity. Your hair grew back, and you felt relatively well for over one year. However, recently you have experienced increased difficulties in breathing, which limit you from performing even mild physical activities. You notice a red lesion on your stomach. Your oncologist recommends that you receive a chest X-ray, which reveals parenchymal nodules. Biopsy of the skin lesion confirms a recurrence of your primary cancer. Your treating physician reviews the following options for your consideration (presented here in brief), noting that therapy is very unlikely to eradicate this cancer:

1. Agent A, administered intravenously, which is associated with alopecia, myelosuppression and neurotoxicity.

2. Agent B, an oral agent, which does not cause the toxicities associate with agent A. However, it may cause pain and redness in the hands and feet that can usually be avoided with dose reductions.

3. A combination chemotherapy regimen consisting of two agents (A and B) that seems to result in a greater likelihood of tumor response than either alone and a modest (a few months) increase in overall survival.

4. Agent C, which is administered intravenously and is associated with alopecia, myelosuppression and neurotoxicity but less overall toxicity than agent A.

There is the general impression that agent A might be more effective than B or C but with more toxicity. Overall, the combination of agents A and B will provide the greatest chance of a tumor response but also the greatest likelihood of toxicity. Agent B is probably the least toxic of these choices, and many research leaders believe that in the long term, it may not make much, or any, difference which of these options is used initially.

Which of these treatment approaches would be most compelling to you in this situation?

In January 2002, as part of a special education initiative associated with the Miami Breast Cancer Conference, our team conducted a national telephone survey of 200 randomly selected oncologists and surgeons. These physicians were presented with dozens of breast cancer clinical scenarios. The results, along with many of the interactive keypad case questions presented during the Miami meeting, are summarized in a special report enclosed with this issue of Breast Cancer Update. A more comprehensive compilation of these data is on BreastCancerUpdate.com.

The following case scenario from interactive keypad polling of attendees at the Miami Breast Cancer Conference is very similar to the clinical situation described above:

Case: A very ill 43-year-old woman presents with lymphangitic lung metastases. She had an ER-negative, HER2-negative breast cancer two years ago and received AC→T adjuvant chemotherapy.

The most common recommendations by oncologists for this case were:

Capecitabine/docetaxel	55%
Anthracycline/taxane	14%
Capecitabine	14%
Vinorelbine	7%
Taxane	5%
Other	4%

In analyzing the patterns of physicians' responses to the theoretical case scenarios, it is fascinating to isolate the effects of specific variables on treatment trends. Age is one such example. At arbitrary cut points, a minimal shift in age sometimes leads to significantly different treatment recommendations. For example, a theoretical case of a 76-year-old woman may lead to much more aggressive treatment recommendations than the case of a 79- or 80-year-old woman. In practice, of course, one assesses the physiologic age in conjunction with the patient's attitude leading to a gestalt that guides patient management.

Seasoned oncologists not only rely on clinical research and research leader opinion, but also on their own clinical experiences with other patients in similar situations. When asked how he taught fellows in training the "art of oncology," Dr Winer paused and replied, "by example."

The data presented in our special report suggests considerable variation in practice patterns. This is not an entirely surprising phenomenon. Experienced oncologists rely on a multitude of factors to shape their decision algorithm. Clinical research and the opinions of leading investigators as well as our own practice experiences dealing with other patients in similar situations all play prominent roles. But what makes the art of oncology so challenging is that there is no "one size fits all" treatment. Each patient is a unique individual whose needs, desires and concerns must be given equal emphasis in the complex equation of treatment selection.

Speaking of size and addressing needs, you will note that one year after relaunching the Breast Cancer Update series with an enhanced CD-containing version, we have enlarged the print supplement, and tinkered with our graphic presentation. Your feedback on these changes and suggestions for future speakers and topics are most welcome.

— Neil Love, MD

Select publications

Patterns of Care in Breast Cancer

Brenin DR et al. **Management of axillary lymph nodes in breast cancer: A national patterns of care study of 17,151 patients.** *Ann Surg* 1999;230:686-91. **Abstract**

Guadagnoli E et al. **Age-related patterns of care: Evidence against ageism in the treatment of early-stage breast cancer.** *J Clin Oncol* 1997;15:2338-44. **Abstract**

Harlan LC et al. **Adjuvant therapy for breast cancer: Practice patterns of community physicians.** *J Clin Oncol* 2002;20:1809-17. **Abstract**

Hyser MJ et al. **Changing patterns of care for occult breast lesions in a community teaching hospital.** *Am Surg* 2000;66:438-42; discussion 442-3. **Abstract**

Mandelblatt JS et al. **Measuring and predicting surgeons' practice styles for breast cancer treatment in older women.** *Med Care* 2001;39:228-42. **Abstract**

Morrow M et al. **Factors influencing the use of breast reconstruction postmastectomy: A National Cancer Database study.** *J Am Coll Surg* 2001;192:1-8. **Abstract**

Morrow M et al. **Factors predicting the use of breast-conserving therapy in stage I and II breast carcinoma.** *J Clin Oncol* 2001;19:2254-62. **Abstract**

Shank B et al. **The 1993-94 patterns of care process survey for breast irradiation after breast-conserving surgery-comparison with the 1992 standard for breast conservation treatment. The Patterns of Care Study, American College of Radiology.** *Int J Radiat Oncol Biol Phys* 2000;48:1291-9. **Abstract**

Stiggelbout AM et al. **Adjuvant chemotherapy in node negative breast cancer: Patterns of use and oncologists' preferences.** *Ann Oncol* 2000;11:631-3. **Abstract**

C Kent Osborne, MD

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Edited comments by Dr Osborne

Results of the ATAC trial: Anastrozole versus tamoxifen versus anastrozole/tamoxifen

This study establishes a new paradigm in blocking the estrogen receptor pathway. It demonstrates that decreasing the estrogen concentration to very low levels is a more potent way to attack the receptor than is tamoxifen.

It is logical that the combination arm in the trial was inferior to the anastrozole arm. Tamoxifen has intrinsic estrogenic activity. Therefore, combining it with an agent that lowers estrogen levels — anastrozole — is counterproductive and gives the same result as with tamoxifen alone.

Clinical applicability of the ATAC trial

I discuss anastrozole with my ER-positive postmenopausal patients. Anastrozole was better than tamoxifen with regard to endometrial cancer, thromboembolic events and hot flashes. Tamoxifen was better with regard to bone fractures. Baseline bone densities will likely be indicated, and I suspect that some women on aromatase inhibitors for long periods of time will need treatment with bisphosphonates. My higher-risk patients will generally receive an aromatase inhibitor, while the lower-risk patients tend to receive tamoxifen — primarily because of the bone issue. I also use aromatase inhibitors in women with a propensity for or history of thrombosis. I believe that as we obtain more data, the aromatase inhibitors will be used more frequently. I talk with patients about anastrozole, because that's the aromatase inhibitor for which we have data.

Potential advantages of bisphosphonates in breast cancer patients

Bisphosphonates will help preserve bone density and reduce the chance of osteoporosis. They may also help as a breast cancer therapy by making the

bones less “fertile soil” for breast cancer cells. Bisphosphonates turn off osteoclast-induced resorption of bone, reduce growth factors and cause apoptosis of tumor cells. These agents may actually be an indirect antitumor therapy.

It will be interesting to see the results of some of the ongoing adjuvant trials using the bisphosphonates, pamidronate and clodronate. Although there is still some inconsistency in the trial results, bisphosphonates likely will be useful agents.

Phase III Randomized Study of Adjuvant Clodronate with or without Systemic Chemotherapy and/or Tamoxifen in Women with Early-stage Breast Cancer **Open Protocol**

Protocol ID: NSABP B-34

Eligibility	Stage I or II breast cancer
ARM 1	Clodronate po qd x 3 years
ARM 2	Placebo po qd x 3 years

Patients may receive adjuvant systemic therapy including tamoxifen at the investigator's discretion.

STUDY CONTACT
Alexander HG Paterson, Ph: 403-670-1707
National Surgical Adjuvant Breast and Bowel Project

Phase III Randomized Study of Zoledronate as Adjuvant Therapy in Patients with Stage I, II or IIIA Nonmetastatic Breast Cancer **Open Protocol**

Protocol ID: SWOG-S9905

Eligibility	Stage I, II or IIIA breast cancer patients with prior or concurrent standard adjuvant systemic therapy
ARM 1	Zoledronate IV q 4 weeks x 2 years
ARM 2	Observation alone x 2 years

Patients must have undergone MRM or BCT plus either ALND or SLNB. Concurrent radiotherapy allowed.

STUDY CONTACT
Charles A Coltman, Jr, Ph: 210-616-5580
Southwest Oncology Group

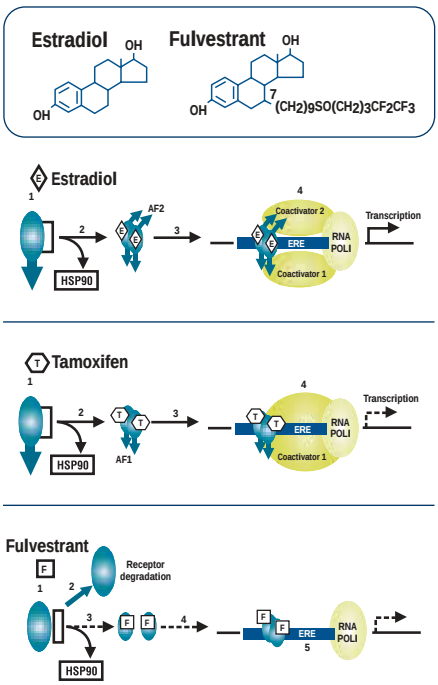
Mechanisms of action of fulvestrant: An estrogen receptor downregulator

If you look at the spectrum of drugs that interact with the estrogen receptor, estrogen is on one end of the spectrum, stimulating most genes under its control after binding to the estrogen receptor. Drugs like tamoxifen stimulate some genes and inhibit others, depending on the tissue and gene. At the far other end of the spectrum, there are drugs like fulvestrant that seem to have a predominantly pure antiestrogenic profile on all genes with none of the agonist qualities of tamoxifen.

There are several activation domains on the estrogen receptor protein — areas that seem to be important in activating transcription of genes.

Tamoxifen only blocks one of these — probably the most important one — but it only blocks one. The other one is still active, and this may give rise to the agonist qualities of tamoxifen.

In contrast, fulvestrant blocks all of the activation domains on the receptor, including both AF-1 and AF-2. Fulvestrant also reduces the level of the estrogen receptor in cells. In some cases, you can't measure any estrogen receptor after exposure to fulvestrant. So, fulvestrant doesn't have any agonist activity, blocks all transcription domains and eliminates the estrogen receptor.



MODE OF ACTION OF ESTRADIOL (E)

1.E binds with high affinity to the estrogen receptor (ER) to form an E-ER complex.
2.The E-ER complex pairs with another E-ER complex (dimerizes) and localizes in the cell nucleus. The two transcription activation functions of ER, called AF1 and AF2, are both active.
3.The E-ER dimer binds to estrogen-sensitive genes at the estrogen response element (ERE).
4.The dimer activates transcription of the estrogen-sensitive gene. (AF1 and AF2 interact with coactivators to stimulate the transcription enzyme RNA polymerase II [RNA POL II].)

MODE OF ACTION OF TAMOXIFEN (T)

1.T binds to ER with low affinity compared with E.
2.The T-ER complex dimerizes and localizes in the cell nucleus, and AF1 (but not AF2) is active.
3.The T-ER dimer binds to the gene DNA at the ERE.
4.Transcription of the estrogen-sensitive gene is lessened because AF2 is inactive and coactivator binding is likewise attenuated. AF1 activity results in the partial agonist activity of T.

MODE OF ACTION OF FASLODEX (F)

1.F binds to ER with affinity similar to E.
2.F triggers rapid degradation of ER.
3.The F-ER complex results in reduced rate of dimerization and nuclear localization.
4.There is reduced binding of F-ER to ERE on the gene resulting in blocked transcription.

Second-line trials for metastatic disease: Fulvestrant versus anastrozole

The European trial and the American trial are a bit different in their structure and results. The American trial — which I think has a better design — was a double-blind study. Patients assigned to anastrozole received placebo injections. Also, because the patients in both groups had to visit the clinic once a month, there was consistency with regard to patient evaluations.

The European trial was not double-blinded. The patients on anastrozole were seen every three months, while the patients on fulvestrant were seen every month. This design has the potential to have some bias in terms of identifying when the patients progressed. Patients in the fulvestrant group of the European trial were seen more often, and conceivably progression would be identified a little earlier than in a patient randomized to anastrozole.

The results show similar response rates between the two drugs. However, in the American trial, the response duration is about twice as long for fulvestrant compared to anastrozole. We have to acknowledge that aromatase inhibitors are very good agents in and of themselves, and in one of these new trials, fulvestrant is at least as good as anastrozole. In the other trial we see an advantage in at least in one important parameter.

Trials 20/21: Phase III Randomized Study of ICI 182780 (Faslodex) versus Anastrozole in Postmenopausal Women with Advanced Breast Cancer (Closed to accrual)

Eligibility	Postmenopausal women with metastatic breast cancer progressing on prior endocrine therapy

ARM 1 | Faslodex 250 mg IM + oral placebo*

ARM 2 | Arimidex 1 mg PO + sham injection*

A third arm in Trial 21, Faslodex 125 mg, was closed after planned analysis demonstrated that predefined efficacy criteria were not met at that dose.

*Only the North American trial (21) had placebo controls.

Tolerability of fulvestrant

This agent is very well tolerated. In clinical trials, the monthly injection didn't cause much pain or discomfort. Both anastrozole and fulvestrant were very well tolerated in the randomized clinical trial. There are theoretical reasons why fulvestrant might not cause hot flashes because it doesn't seem to cross the blood-brain barrier. In these studies, the rate of hot flashes and other side effects with both fulvestrant and anastrozole was very low.

We know very little about fulvestrant's effect on bone and lipids. These pure antiestrogens could theoretically be deleterious, which is not as important for metastatic breast cancer as it will be if this agent moves into adjuvant therapy and prevention. Additional studies are needed to clarify these issues, some of which can be dealt with by using other therapies. For example, in patients with low bone density, bisphosphonates could theoretically be used. In the end, if it is a much better cancer drug, these concerns will be secondary.

Trials 20 and 21: Study Design Differences

	Trial 20 (European)	Trial 21 (North American)
Receptor unknown	Allowed	Not allowed
Double-blind	No	Yes
Multi-institutional	Europe, Australia, South America	North America
Multiple dose levels	No	Yes, initially
Dosing	Single injection	Divided injections
Evaluations - fulvestrant	Monthly	Every three months
Evaluations - anastrozole	Every three months	Every three months

Reproduced with permission from a presentation by Robert W Carlson, MD

Fulvestrant in the adjuvant setting

Adjuvant trials of fulvestrant are in the planning stage. If the data that become available continue to look promising, I believe fulvestrant will move forward into the adjuvant situation. In almost every cancer therapy, we see greater benefits in the adjuvant setting than in the metastatic setting. We are seeing this with anastrozole now — it doesn't cure metastatic disease, but in the adjuvant situation with micrometastatic disease, the effects are much greater. The effects of fulvestrant that we might see in the adjuvant situation are likely to be much greater than in the metastatic setting.

Combining fulvestrant and anastrozole

It would be intriguing to combine fulvestrant with an aromatase inhibitor. This would reduce the ligand, estradiol, to a very low level, and it would deplete the estrogen receptor. I believe a large randomized trial — comparing an aromatase inhibitor versus fulvestrant versus the combination — will be done.

The combination arm of the ATAC trial yielded a worse outcome than anastrozole alone. This makes some biological sense because of tamoxifen's partial estrogen agonist activity. However, when fulvestrant binds the receptor, there is a different outcome than with tamoxifen. When we examine the differences in these drugs at the molecular level, it is logical that the combination of fulvestrant and anastrozole may be effective.

Biology of HER2-positive, ER-positive tumors

The estrogen receptor pathway is not as simple as we once thought. An important component to estrogen's growth-stimulating effects on tumors that have amplification of the HER2 oncogene involves growth factor pathways. Growth factors can phosphorylate and activate the estrogen receptor and the estrogen receptor coactivator AIB-1. When these are activated, SERMs like tamoxifen are converted into potent estrogens with very little antagonist activity.

Our laboratory studied HER2 and AIB-1 levels in human tumors. The data show that tumors with high levels of AIB-1, estrogen receptor and HER2 don't benefit from tamoxifen. This clinical data provides a rationale to inhibit these growth factor pathways. There is evidence that blocking the growth factor receptor with agents such as Iressa® (ZD 1839) or trastuzumab prevents tamoxifen-stimulated growth and restores tamoxifen's antagonistic activity.

HER2-positive, ER-positive patients generally don't benefit from endocrine therapy as much as HER2-negative, ER-positive women. However, we're only measuring one component with HER2 status. In our study, only tumors with high levels of both AIB-1 and HER2 lack response to tamoxifen. Patients with high HER2 levels but low AIB-1, or high AIB-1 but low HER2, benefit from tamoxifen. Approximately 60% of tumors that overexpress HER2 also overexpress AIB-1. Therefore, 10 to 15 percent of tumors express both. In my own practice, I give ER-positive, HER2-positive patients endocrine therapy, knowing that some patients won't benefit.

Treating the ER-positive, HER2-positive patient

In the past, I used tamoxifen in these women, but now I tend to use aromatase inhibitors. Data from my own laboratory show that HER2 overexpressing tumors respond much better to estrogen deprivation than to

Select publications

Fulvestrant (ICI 182,780; Faslodex®)

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Cheung KL, Robertson JF. **Fulvestrant**. *Expert Opin Investig Drugs* 2002;11:303-308. **Abstract**

Cicatiello L et al. **The antiestrogen ICI 182,780 inhibits proliferation of human breast cancer cells by interfering with multiple, sequential estrogen-regulated processes required for cell cycle completion.** *Mol Cell Endocrinol* 2000;165:199-209. **Abstract**

Curran M, Wiseman L. **Fulvestrant**. *Drugs* 2001;61:807-13; discussion 814. **Abstract**

Elkak AE, Mokbel K. **Pure antiestrogens and breast cancer.** *Curr Med Res Opin* 2001;17:282-9. **Abstract**

England GM, Jordan VC. **Pure antiestrogens as a new therapy for breast cancer.** *Oncol Res* 1997;9:397-402. **Abstract**

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Gradishar WJ, Jordan VC. **Clinical potential of new antiestrogens.** *J Clin Oncol* 1997;15:840-52. **Abstract**

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Howell A et al. **Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer.** *Lancet* 1995;345:29-30. **Abstract**

Hu XF et al. **Circumvention of tamoxifen resistance by the pure antiestrogen ICI 182,780.** *Int J Cancer* 1993;55:873-6. **Abstract**

Jones S. **Fulvestrant ('Faslodex®') versus anastrozole ('Arimidex®') for the treatment of advanced breast cancer in postmenopausal women — safety update on the combined analysis of two multicenter trials.** *Breast Cancer Res Treat* 2001;**Abstract 455.**

Long BJ et al. **The steroidal antiestrogen ICI 182,780 is an inhibitor of cellular aromatase activity.** *J Steroid Biochem Mol Biol* 1998;67:293-304. **Abstract**

Lu Q et al. **The effect of combining aromatase inhibitors with antiestrogens on tumor growth in a nude mouse model for breast cancer.** *Breast Cancer Res Treat* 1999;57:183-92. **Abstract**

Mauriac L. **Fulvestrant ('Faslodex®') is effective in advanced breast cancer in postmenopausal patients with visceral metastases: Comparison with anastrozole.** *Breast Cancer Res Treat* 2001;**Abstract 452.**

McClelland RA et al. **Enhanced epidermal growth factor receptor signaling in MCF7 breast cancer cells after long-term culture in the presence of the pure antiestrogen ICI 182,780 (Faslodex).** *Endocrinology* 2001;142:2776-88. **Abstract**

McClelland RA et al. **Short-term effects of pure antioestrogen ICI 182,780 treatment on oestrogen receptor, epidermal growth factor receptor and transforming growth factor-alpha protein expression in human breast cancer.** *Eur J Cancer* 1996;32A:413-6. **Abstract**

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Osborne CK. **A double-blind randomized trial comparing the efficacy and tolerability of Faslodex™ (fulvestrant) with Arimidex™ (anastrozole) in postmenopausal (PM) women with advanced breast cancer (ABC).** *Breast Cancer Res Treat* 2000;64(1):Abstract 7.

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Robertson JF. **Estrogen receptor downregulators: New antihormonal therapy for advanced breast cancer.** *Clin Ther* 2002;24 Suppl A:A17-30. **Abstract**

Robertson JF. **Faslodex (ICI 182,780), a novel estrogen receptor downregulator, future possibilities in breast cancer.** *J Steroid Biochem Mol Biol* 2001;79:209-12. **Abstract**

Robertson JF. **ICI 182,780 (Fulvestrant)—the first oestrogen receptor down-regulator—current clinical data.** *Br J Cancer* 2001;85 Suppl 2:11-4. **Abstract**

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Eric P Winer, MD

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Vice Chair, CALGB Breast and Cancer Control and Health Outcomes Committees

Executive Committee Member, National Surgical Adjuvant Breast and Bowel Project (NSABP)

Vice Chair, American Society of Clinical Oncology, Health Services Research Committee

Member, National Cancer Care Network Breast Cancer Care Guidelines Committee

Edited comments by Dr Winer

Less toxic regimens for metastatic breast cancer

Throughout the 1990s, the focus in breast cancer research was on high-dose chemotherapy and dose-intensive regimens. Clearly, the pendulum has now swung in a different direction. Over the course of the last decade, we have learned that more is not necessarily better. There has been tremendous interest in identifying more tolerable regimens that may also be more effective, with a focus on targeted therapies.

We have conducted a number of trials taking advantage of oral dosing schedules and low-dose weekly schedules. These trials not only allow women to have their cancer under control but also to lead as normal a life as possible. First and foremost, we would like to cure every woman's breast cancer, but if we cannot do that, then the least we can do is help women live longer without suffering severe treatment-related toxicities.

We have come a long way in terms of making life more tolerable for women with advanced breast cancer. Not long ago, patients would spend much more time in the hospital either receiving chemotherapy or recovering from its toxicities. We have moved away from that type of approach. Although a small number of women may benefit from high-dose chemotherapy, studies have not demonstrated an overall benefit. In fact, single-agent chemotherapy may be as effective as combination chemotherapy.

Of course, some combination chemotherapy regimens are associated with higher response rates, but sequential single-agent chemotherapy is probably associated with the same overall survival. Single-agent chemotherapy allows us to tailor the treatment to the individual woman. The ability to combine the newer biologic agents with single-agent chemotherapy is another advantage.

Quality and duration of life in metastatic breast cancer

In the treatment of women with metastatic breast cancer, the two most important considerations are the quality and duration of life. For those receiving chemotherapy, their quality of life is a balance between disease control and treatment-related toxicity. In women with tumor-related symptoms, quality of life is mainly determined by tumor control. In the capecitabine/docetaxel (XT) trial, a survival benefit was associated with the XT combination compared to docetaxel alone; however, relatively few patients in the docetaxel arm later received capecitabine. To me, what this trial demonstrates is that capecitabine is an excellent agent for breast cancer.

Capecitabine in clinical practice

I use a lot of single-agent capecitabine fairly early in the management of women with metastatic breast cancer. In fact, outside of a clinical trial, I almost exclusively use it as a single agent. In metastatic disease, there is no specific order in which to give chemotherapeutic agents. Since women stay on their first- or second-line treatments longer than their third- and fourth-line treatments, it makes sense to use the more tolerable agents earlier.

Therefore, outside of a clinical trial, I frequently give capecitabine as either first- or second-line therapy. In order to minimize toxicities, I usually start with a dose of 2,000 mg/m^2 in two divided doses for two weeks followed by one week off therapy. There is concern about the hand-foot syndrome and diarrhea associated with capecitabine, but if one is attentive to the dose and educates patients about stopping treatment if they experience side effects, it is very well tolerated.

Capecitabine and quality of life

In addition to its role in taxoid-resistant breast cancer, capecitabine may be useful as second-line therapy in anthracycline-resistant metastatic breast cancer or as first-line treatment as an alternative to intravenous chemotherapy. The improvement of patients' quality of life achieved by using oral agents with similar efficacy but enhanced tolerability is a vital component of the care of cancer patients where the goal of treatment is palliation. Furthermore, the low incidence of myelosuppression makes capecitabine an attractive agent for use in the adjuvant setting and also for incorporation into combination regimens, either with conventional agents, for example epirubicin/doxorubicin, or agents such as the taxoids and vinorelbine.

EXCERPT FROM: Leonard RCF. *Br J Cancer* 2001;84(11):1437-42. **Abstract**

Patient preference for oral versus intravenous chemotherapy

As long as it does not increase toxicity or compromise efficacy, most patients prefer the oral route of administration. Geoffrey Liu conducted a patient preference study, which questioned patients about their preferences for oral or intravenous chemotherapy. If it provided similar efficacy and fewer side effects, 90% of the patients would choose oral chemotherapy.

Prospective Evaluation of Patient Preferences for Palliative Chemotherapy

Patient preference for method of administration	
ORAL	92/103 (89%)
reasons for preference	
convenience	57%
problems with IV/needles	55%
prefer home administration	33%
INTRAVENOUS	10/103 (10%)
NO PREFERENCE	1/103 (1%)
Impact of efficacy on choice (regardless of initial preference)	
Unwilling to accept lower response rates	70%
Unwilling to accept shorter duration of response	74%
Patient preference for decision-making	
Patients having a preference	99%
patient makes choice	38%
physician makes choice	39%
shared choice	22%

Patient preferences were not associated with age, gender, site of primary cancer or previous CT experiences.

Derived from Liu et al. *J Clin Oncol* 1997;15:110-15. **Abstract**

First-line chemotherapy in women who have received an anthracycline as adjuvant therapy

Outside of a clinical trial, a woman who has received an anthracycline as adjuvant therapy could potentially receive either docetaxel, paclitaxel, capecitabine or vinorelbine as first-line therapy for metastatic disease. In my opinion, the response rates for these agents are fairly similar. Some believe docetaxel is the most active agent, but I am not convinced that any of these agents have different activity. I tailor the treatment to the woman and base my decision on the types of side effects the woman would prefer to avoid.

From a toxicity standpoint, the best agents are probably capecitabine and vinorelbine. Alopecia is often an issue for women, and capecitabine is not associated with hair loss. If one is careful with the capecitabine dose, most side effects can be avoided. Over time, some women may experience chronic changes in their hands and feet, but that is the predominant toxicity encountered with capecitabine. In women without rapidly progressive disease, I frequently use capecitabine.

Choice of systemic agents for metastatic breast cancer

Until recently, the treatment alternatives to taxoids were very limited. However, results from studies in advanced breast cancer of the new, oral, enzymatically activated fluoropyrimidine, capecitabine, indicate that this agent may be useful when anthracycline-based chemotherapy fails as well as in taxoid failures. Capecitabine may offer an effective, well-tolerated and more convenient alternative to taxoids and other intravenous cytotoxic agents. Clinical trials of capecitabine in breast cancer have demonstrated substantial activity with durable responses and meaningful clinical benefits.

EXCERPT FROM: Leonard RCF. *Br J Cancer* 2001;84(11):1437-42. **Abstract**

Rapidly progressing metastatic breast cancer

Combination chemotherapy may make more sense in this situation, particularly if I believe that the woman realistically has only one chance to improve. This is also the sole situation in which I would combine chemotherapy with hormonal therapy for a woman with estrogen receptor-positive disease. Although I may have concerns about combination chemotherapy in a woman with a poor performance status, I would probably use it. This is actually the type of situation where I would consider agents like doxorubicin, the taxanes or the capecitabine / docetaxel combination.

Management of women with metastatic hormone receptor-positive breast cancer

Since hormonal therapy is better tolerated than chemotherapy, most women with metastatic hormone receptor-positive breast cancer should initially receive hormonal therapy. Responses to hormonal therapy are often durable, and women are usually better off waiting to receive more toxic therapy.

There are exceptions to this rule, especially in women with very rapidly or moderately rapidly progressing disease. These women have a below average chance of responding to hormonal therapy. In the past, it was speculated that it might take longer to respond to hormonal therapy than chemotherapy.

Perhaps chemotherapy provides a little faster response than hormonal therapy, but we probably made that more of an issue than necessary.

It may be time to challenge the assumption that the presence of visceral metastases decreases the likelihood of responding to hormonal therapy. Visceral metastases in 2002 are quite different than those in 1975. In 1975, a woman who had liver metastases often had a very large liver, abnormal liver function tests and elevated bilirubin. In 2002 many of those lesions are seen on a spiral CT, and frequently these may be 1-2 centimeters, entirely asymptomatic and with normal liver function tests.

Management of women with metastatic HER2-positive breast cancer

Even though there is suggestive evidence that women with HER2-positive, ER-positive breast cancers may be less likely to respond to hormonal therapy, I would still consider using it. When it is time to advance to chemotherapy in women with HER2-positive breast cancer, trastuzumab is the standard of care. Whether or not to combine trastuzumab with chemotherapy is the only remaining question. Since the response rates and the control of tumor-related symptoms are higher for trastuzumab plus chemotherapy, oncologists commonly administer the combination. Additionally, the survival benefit seen with trastuzumab in the pivotal trial by Slamon and colleagues was obtained when chemotherapy and trastuzumab were given together.

Trastuzumab monotherapy

There are a few situations in which trastuzumab may be used alone. First is the woman who wishes to avoid chemotherapy-related side effects. The second situation involves the woman with fairly minimal disease or disease that is progressing slowly. Another situation involves the woman who received adjuvant AC/paclitaxel and three months later has recurrent disease. This woman has demonstrated fairly chemotherapy-resistant disease, and her chance of improving is dependent upon her response to trastuzumab. It may be worth thinking about trastuzumab alone in this type of woman, although in the end I probably would also use chemotherapy.

Trastuzumab plus chemotherapy

For the time being, trastuzumab should not be given with an anthracycline because of the potential cardiotoxicity. The standard of care is trastuzumab plus paclitaxel. Given the activity of docetaxel in women with metastatic breast cancer and the potential preclinical synergy, there are many physicians who administer trastuzumab plus docetaxel.

Approximately three years ago, we started studying trastuzumab plus vinorelbine. In our first phase II study with 40 women, trastuzumab plus vinorelbine was well tolerated with an overall response rate of 75%. There is an on-going multicenter phase III trial, with 50 sites in the United States, comparing vinorelbine / trastuzumab to a taxane / trastuzumab regimen.

Vinorelbine has not traditionally been considered a first-line agent for the treatment of metastatic breast care; however, vinorelbine / trastuzumab is a promising regimen. I predict that the efficacy between the two arms will be fairly similar, and the toxicity with the vinorelbine / trastuzumab arm will be lower.

Trastuzumab/vinorelbine for HER2-overexpressing metastatic breast cancer

The overall response rate was 75%, with a suggestion of higher response rates observed in subgroups of patients with HER2 +3 positive tumors, and among patients receiving the combination regimen as first-line chemotherapy for metastatic breast cancer. Response rates in excess of 60% were observed for patients receiving the regimen as second- or third-line therapy for metastatic cancer, and among patients who had previously received anthracycline- and taxane-based chemotherapy. Acute toxicities were quite mild and manageable. Neutropenia was the most common severe toxicity and was managed with vinorelbine dose modification without other sequelae. Gastrointestinal side effects and alopecia were modest. Sustained therapy with vinorelbine and trastuzumab was feasible without encountering cumulative side effects. A small percentage of patients were taken off study for asymptomatic declines in left ventricular EF.

EXCERPT FROM: Burstein HJ et al. *J Clin Oncol* 2001;19(10):2722-30.

There are both US and European trials evaluating the combination of capecitabine and trastuzumab, which could potentially be a well-tolerated regimen. Anecdotally, I have seen a number of good responses to single-agent capecitabine in women with HER2-positive disease who have failed trastuzumab.

Therapy for women progressing on a trastuzumab/chemotherapy regimen

Although I sometimes continue trastuzumab after a woman progresses, there is no clear evidence that it is beneficial. MD Anderson is conducting a trial to compare vinorelbine to vinorelbine / trastuzumab in women who progress after taxane / trastuzumab combination therapy.

In the nonprotocol setting for a woman who progresses on trastuzumab, I tend to use it once more. Women often feel very strongly about continuing trastuzumab, particularly if they have had a response. In patients who have responded to a trastuzumab-containing regimen, at the time of disease progression, I typically try one more trastuzumab-containing regimen or stop the trastuzumab and then come back to it later on.

One exception is the woman who responds to a trastuzumab-containing regimen and then develops CNS metastases. I consider that woman to have progressive disease in the brain but not trastuzumab-refractory disease. Therefore, I would continue the same regimen and treat her CNS disease with cranial irradiation.

Serum versus CSF levels of trastuzumab

It is unknown whether and to what extent trastuzumab can cross the blood-brain barrier. Therefore, we measured CSF and concomitant serum levels of trastuzumab in a 62-year-old patient with meningeal carcinomatosis treated with weekly intravenous trastuzumab. A few hours after trastuzumab infusion, serum levels achieved were as expected in the range of 10,000 to 100,000 ng/mL. Concomitant CSF levels were 300-fold lower. Despite a possibly leakier blood-brain barrier in this patient with meningeal carcinomatosis, only minimal amounts of trastuzumab penetrated the CSF. Therefore, it is unlikely that intravenous trastuzumab would be useful to treat meningeal or cerebral disease of breast cancer.

EXCERPT FROM: Pestalozzi BC, Brignoli S. *J Clin Oncol* 2000;18(11):2350-51.

CNS progression during a phase II study of docetaxel/trastuzumab in HER2-positive metastatic breast cancer

Three patients had CNS progression after an initial response to therapy. These patients were withdrawn from the study. In two of these patients, the CNS was the first and only site of disease progression. These patients continued to receive trastuzumab therapy after whole-brain irradiation and remained without evidence of other systemic progression outside the CNS for 4 and 12 months. The CNS seems to be a sanctuary for disease in patients treated with trastuzumab and docetaxel therapy. This could be due in part to the low penetration of trastuzumab and the taxanes into the brain.

EXCERPT FROM: Esteva FJ et al. *J Clin Oncol* 2002;1800-1808.

Trastuzumab schedule

Although the approved schedule is weekly, Canadian trials have evaluated an every-three-week schedule both as a single-agent and in combination with paclitaxel. There also has been discussion about changing the Intergroup adjuvant trial to an every-three-week schedule.

When combined with chemotherapy, I still administer trastuzumab on a weekly schedule. In order to make life easier, I have used the every-three-week schedule for a few women receiving trastuzumab alone, and it has been well tolerated. We will probably see new regimens with an every-three-week schedule for chemotherapy and trastuzumab.

Schedule of trastuzumab

The half-life of trastuzumab seems to be longer than originally reported, and studies are underway to define it accurately. A longer half-life means that dosing less frequently than every three weeks may also be feasible. To this end, modelling based on known pharmacokinetic data is being used to assess the feasibility of novel dosing regimens. This process aims to identify regimens involving the administration of trastuzumab-loading doses on consecutive days to generate therapeutic concentrations within a shorter time. Furthermore, the longer half-life means that longer drug-free intervals (six or eight weeks) may be possible between maintenance doses. For example, a regimen involving the administration of trastuzumab 8 mg/kg on three consecutive days followed by 8 mg/kg every six weeks may be feasible. The associated greater dosing flexibility is predicted to improve management of patients further by offering more choice and convenience, including drug holidays.

EXCERPT FROM: Leyland-Jones B. *Lancet Oncol* 2002;3(3):137-44. **Abstract**

The patient-physician relationship

When patients are sick and need more medical care, the relationship with their doctor, nurse and social worker becomes more important in terms of quality of life. I try to make decisions with the patients and to provide them with options so they can guide me. Decision-making is about describing the options, knowing your patient and then trying to pick the best option together. Communication is very important. The challenge we all face is being realistic so that patients do not have unrealistic expectations but also have a real sense of hopefulness.

Patient-physician decision-making in breast cancer

Despite the increase in consumerism, many breast cancer patients come to consultations with little or no prior knowledge of breast cancer and want their physicians to choose on their behalf. In breast cancer, many alternatives do not differ in their impact on survival and recurrence but do have very different side effects. In adjuvant therapy, some patients must trade-off the long-term effects of chemotherapy (e.g., infertility and so on) with a small survival difference. Physicians who assume the responsibility for choosing on behalf of their patients need to be able to understand their patients' preferences. With limited time and resources, physicians need to synthesize their patient's detailed medical history along with the relevant evidence from the literature and incorporate their patients' preferences. This is a challenging task to complete in a short visit, even for the most skilled practitioners.

Physicians need to be prepared to handle the diversity of their patients. In particular, physicians need to be able to engage and empower their patients to participate in the consultation in whatever manner is most comfortable for the patient.

EXCERPT FROM: Sepucha KR et al. *J Clin Oncol* 2000;18(6):1230-8.

ATAC trial results

I was surprised by the ATAC trial results, since I was predicting the three arms, in short-term follow-up, would be equivalent with perhaps differences in toxicity. Based on studies in postmenopausal women with advanced disease, the aromatase inhibitors may be better than tamoxifen. On preliminary and early follow-up, the ATAC trial would also suggest that anastrozole is better than tamoxifen or the combination in terms of disease-free survival.

Applying these results to clinical practice will be a challenge. In women receiving tamoxifen for more than one or two months, I would not switch to an aromatase inhibitor. Whether I will use anastrozole in every postmenopausal woman in whom I would have given tamoxifen is the pressing issue. In terms of selecting an aromatase inhibitor in the adjuvant setting, I am data-driven, and at this point in time I would use the results of the ATAC trial and prescribe anastrozole. Undoubtedly, there will be much discussion about the applicability of these results to the other aromatase inhibitors.

Select publications

Quality of life and decision-making in patients with metastatic breast bancer

Bergh J et al. **A systematic overview of chemotherapy effects in breast cancer.** *Acta Oncol* 2001;40:253-81. **Abstract**

Bruera E et al. **Treatment decisions for breast carcinoma. Patient preferences and physician perceptions.** *Cancer* 2002;94:2076-80. **Abstract**

Butow PN et al. **Psychosocial predictors of survival: Metastatic breast cancer.** *Ann Oncol* 2000;11:469-74. **Abstract**

Coates AS et al. **Quality-of-life scores predict outcome in metastatic but not early breast cancer. International Breast Cancer Study Group.** *J Clin Oncol* 2000;18:3768-74. **Abstract**

Danova M et al. **Strategies of medical treatment for metastatic breast cancer.** *Int J Oncol* 2001;19:733-9. **Abstract**

Geels P et al. **Palliative effect of chemotherapy: Objective tumor response is associated with symptom improvement in patients with metastatic breast cancer.** *J Clin Oncol* 2000;18:2395-405. **Abstract**

Goodwin PJ et al. **The breast expressive-supportive therapy (BEST) study: An RCT of the effect of group psychosocial support on survival in metastatic breast cancer.** *Proc ASCO* 2001;**Abstract 79.**

Grunfeld EA et al. **Chemotherapy for advanced breast cancer: What influences oncologists' decision-making?** *Br J Cancer* 2001;84(9):1172-8. **Abstract**

Olin JJ, Muss HB. **New strategies for managing metastatic breast cancer.** *Oncology (Huntingt)* 2000;14:629-41; discussion 642-4, 647-8. **Abstract**

Osoba D et al. **Effect of treatment with HER2mab (trastuzumab/Herceptin™) plus chemotherapy (H+C) versus chemotherapy alone (C) on health-related quality of life (HRQL) in women with HER2/neu-overexpressing metastatic breast cancer.** *Proc ASCO* 2001;**Abstract 109.**

Perez EA. **Metastatic bone disease in breast cancer: The patient's perspective.** *Semin Oncol* 2001;28:60-3. **Abstract**

Sepucha KR et al. **Building bridges between physicians and patients: Results of a pilot study examining new tools for collaborative decision-making in breast cancer.** *J Clin Oncol* 2000;18(6):1230-8. **Abstract**

Stockler M et al. **Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer.** *Cancer Treat Rev* 2000;26:151-68. **Abstract**

Titzer ML et al. **Clinicians' assessment of quality of life (QOL) in outpatients with advanced cancer: How accurate is our prediction? A Hoosier Oncology Group study.** *Proc ASCO* 2001;**Abstract 1532.**

Varma G et al. **The goal of chemotherapy: Little agreement between patients and their doctors.** *Proc ASCO* 2001;**Abstract 1542.**

Wilson KA, Dowling AJ, Abdolell M, Tannock IF. **Perception of quality of life by patients, partners and treating physicians.** *Qual Life Res* 2000;9:1041-52. **Abstract**

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ATAC trial

The standard adjuvant hormonal therapy, tamoxifen, has been very effective in reducing the breast cancer recurrence rate. The main objective of the ATAC trial was to compare the efficacy and safety of adjuvant anastrozole, which lowers estrogen levels, and tamoxifen. A second objective of this trial was to determine if the combination of anastrozole plus tamoxifen would further reduce the recurrence risk or alter the safety profile associated with the individual agents.

Overall efficacy

After two and one-half years of follow-up, the ATAC trial demonstrated that anastrozole further reduced the risk of recurrence compared to tamoxifen. The estrogen receptor status was known for 83% of the women. In estrogen receptor-positive women, there was a 22% reduction in the risk of recurrence with anastrozole compared to tamoxifen. For the group as a whole — including estrogen receptor-negative and receptor-unknown patients — there was a 17% reduction in the risk of recurrence with anastrozole relative to tamoxifen.

Additionally, there was a 58% reduction in the risk of contralateral and ipsilateral breast cancers with anastrozole compared to tamoxifen. There was no additional reduction in the risk of recurrence for the combination of anastrozole and tamoxifen compared to tamoxifen alone. My personal bias is that eventually there will be an increase in survival associated with anastrozole.

Adjuvant anastrozole in women receiving chemotherapy

Approximately 20% of the women in the ATAC trial received adjuvant chemotherapy. The question remains as to whether these women will derive similar benefits from anastrozole. Participation in the trial was delayed until these women finished their systemic chemotherapy. We are now evaluating that subpopulation in more detail. I do not think chemotherapy negates anastrozole's effects.

Anastrozole plus tamoxifen combination

ATAC was an elegant study, and if there was going to be any synergistic or additive benefit to combined hormonal therapy in breast cancer, this was an ideal setting. The combination arm was slightly inferior to tamoxifen and clearly inferior to anastrozole. Tamoxifen totally negated the effects of anastrozole. For estrogen-dependent tumors in an estrogen-deprived environment, it has been speculated that tamoxifen acts like an agonist.

Overall safety profiles

Tamoxifen, because of its agonistic properties, increases the risk of thromboembolic events, vaginal spotting and bleeding, vaginal discharge and endometrial cancer. All of these side effects were less common with anastrozole than tamoxifen. Compression fractures of the spine, wrist fractures and rib fractures occurred more frequently with anastrozole than tamoxifen.

On the other hand, the risk of hip fractures was identical for anastrozole and tamoxifen. There was also a slight increase in the occurrence of arthralgias associated with anastrozole. In the metastatic setting, only an occasional woman will have discomfort requiring an NSAID. I have not seen any women in whom the arthralgias required a change or discontinuation of therapy. The anastrozole plus tamoxifen combination did not modify the safety profile of these agents compared to tamoxifen alone.

Bone density

A subprotocol of the ATAC trial is systematically evaluating the turnover of bone markers and the changes in bone density. This data will be available in the next few months. Since anastrozole further reduces estrogen levels in postmenopausal women by 95-98%, I personally believe that anastrozole increases bone loss beyond that which normally occurs in postmenopausal women.

Although this is a real side effect, you can monitor women for changes in bone density and institute therapeutic interventions when needed. In my clinic, many women are already on a bisphosphonate — calcitonin or calcium

supplements to reduce the risk of osteoporosis. When prescribing anastrozole as adjuvant therapy, baseline and periodic bone densities are indicated. If there is a decrease in bone density, it would be appropriate to begin interventional therapy.

Weight gain

There was less weight gain associated with anastrozole than tamoxifen. Data from NSABP P-1 did not show any change in weight for tamoxifen compared to placebo. The ATAC trial, however, demonstrated some weight gain associated with tamoxifen and no substantial change in weight associated with anastrozole. A majority of women with breast cancer — even those receiving chemotherapy — gain some weight.

Interchangeability of the aromatase inhibitors

A very important question that needs to be addressed is the interchangeability of the available aromatase inhibitors — anastrozole, letrozole and exemestane — in the adjuvant setting. Right now, there is only data with anastrozole. The other two agents are available for use by physicians, but there is no safety and efficacy data for them in the adjuvant setting. I have a reservation about saying that this is a class effect and in switching to another aromatase inhibitor for which we do not have any data.

Selection of aromatase inhibitors as adjuvant therapy

Many reviewers have attempted to draw indirect comparisons between drugs within this class of aromatase inhibitors in an effort to identify the optimal aromatase inhibitor… .

This is fraught with difficulties, because randomized, controlled trials involving these agents have study designs with different criteria and different methods of assessment in different patient populations. As a result, such indirect comparisons between trials cannot possibly lead to a clear outcome in favor of any single drug. Some investigators even have attempted to reach conclusions based on the degree of estrogen suppression exhibited by aromatase inhibitors, but it should be noted that the net clinical relevance of plasma estrogen reduction still needs to be carefully evaluated. . . .

There are differences in both the chemistry and the pharmacological properties of the newer-generation aromatase inhibitors. These differences seem to have an impact upon selectivity of the drugs for aromatase (e.g., effect on adrenocorticotropic hormone-stimulated cortisol levels) and may possibly have an effect on the clinical efficacy of aromatase inhibitors in the adjuvant setting on a long-term basis.

EXCERPT FROM: Buzdar A, Howell A. *Clin Cancer Res* 2001;7:2620-35. **Abstract**

Clinical implications of the ATAC trial

The ATAC trial was designed to evaluate women who were just starting adjuvant hormonal therapy. In those women, we must discuss that we now have an agent — anastrozole — which appears to have a better safety and efficacy profile than tamoxifen. If I were the patient, I would go with the newer therapy — anastrozole — even though there is a shorter follow-up.

We would like all drugs to have follow-up for 20-30 years, but we cannot wait 20-30 years for the data to mature. We must provide women with the information and guide them as to the strengths and weaknesses of the data. The primary shortcoming of the ATAC trial data is its relatively short follow-up. On the other hand, the strengths of the data are the significant reduction in the risk of recurrence and the fewer side effects associated with anastrozole.

The ATAC trial does not address the woman who is free of recurrence and is already receiving adjuvant tamoxifen. Generally, a switch to an aromatase inhibitor should be considered only if a woman is experiencing substantial toxicity from tamoxifen. I would not — across the board — switch women who are tolerating tamoxifen. There are ongoing studies evaluating whether an aromatase inhibitor can further reduce the risk of recurrence in women who have received two or more years of adjuvant tamoxifen.

Implications of the ATAC results to breast cancer prevention trials

The dramatic reduction in second breast cancers observed with anastrozole in the ATAC trial has tremendous implications for breast cancer prevention. The Europeans are already planning to compare the efficacy of anastrozole and tamoxifen in high-risk women and in women with DCIS. We need to explore this further with definitive studies, particularly because postmenopausal women are at increased risk for thrombosis and endometrial cancer with tamoxifen.

The ATAC trial results clearly demonstrate that anastrozole has a much better safety profile than tamoxifen. The main safety concerns associated with tamoxifen — thromboembolic complications, vaginal bleeding, vaginal discharge and endometrial cancer — are related to its agonistic properties. A woman experiencing vaginal bleeding has to undergo a number of tests and procedures before we can rule out endometrial cancer. In the preliminary analysis of the ATAC trial results, vaginal bleeding was almost nonexistent with anastrozole; therefore, it is an attractive agent to evaluate for breast cancer prevention.

Adjuvant and neoadjuvant capecitabine/docetaxel (XT) trial

In the metastatic setting, capecitabine / docetaxel (XT) has demonstrated both survival and response rate advantages. Therefore, we plan to compare the XT combination and a taxane in terms of the ability to reduce the risk of

recurrence in the adjuvant and neoadjuvant setting.

Patients will be randomized to either weekly paclitaxel for 12 weeks or three cycles of XT. Both regimens will be followed by four cycles of FAC. We chose weekly paclitaxel as our control arm, because of our prospective trial demonstrating that weekly neoadjuvant paclitaxel resulted in twice as many pathological complete responses as every-three-week paclitaxel. There is less data indicating that docetaxel is schedule-dependent.

We are going to use 75 mg/m^2 of docetaxel and 1250 mg/m^2 of capecitabine administered orally twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for two weeks followed by a one-week rest period given as three-week cycles.

We hope the toxicity will be manageable through capecitabine dose reductions. We have appropriate dose modification criteria for nonhematologic toxicity. If there is a neutropenic fever, we plan to add growth factors.

Women with an intact breast primary will receive a taxane as part of their therapy up front. We will determine if more women in the XT arm have a pathological complete response and breast preservation. Our previous experience indicates that women with pathological complete responses do very well in the long run. Therefore, a study arm with a higher pathological complete response rate will have fewer recurrences and disease-related morbidities or deaths.

Since XT has a higher likelihood of causing objective regression, I think more women receiving the combination will have a pathological complete response. There are a number of secondary end points in the study. In women with an intact primary, we will have the initial tumor and, subsequently, we can study what happens at the cellular or molecular level.

Experimental data indicate that docetaxel upregulates thymidine phosphorylase. To correlate this with outcome and response, we will be measuring these types of tumor factors at baseline and after therapy.

NSABP B-27: Neoadjuvant AC versus AC → docetaxel

This trial clearly demonstrated that neoadjuvant, alternating, noncross-resistant chemotherapy regimens reduce the breast cancer volume. Women receiving docetaxel had almost twice as many pathological complete responses and more breast preservation than those receiving only four cycles of AC. I believe that once the data matures, more women receiving the docetaxel/AC combination will be alive and free of disease than those receiving AC alone.

Phase III Randomized Study of Preoperative Doxorubicin and Cyclophosphamide (AC) Versus Preoperative AC Followed by Docetaxel Versus Preoperative AC and Postoperative Docetaxel in Women with Operable Carcinoma of the Breast **Closed Protocol**

Protocol ID: NSABP B-27

Eligibility	Clinically palpable, > 1 cm, node-negative and node-positive breast cancer
ARM 1	AC x 4 + TAM → SURGERY
ARM 2	AC x 4 + TAM + T x 4 → SURGERY
ARM 3	AC x 4 + TAM → SURGERY → T x 4

AC=doxorubicin/cyclophosphamide; T=docetaxel; TAM=tamoxifen x 5 years

* Patients undergoing breast-conserving surgery receive radiotherapy.

PRELIMINARY RESULTS OF NSABP B-27: PREOPERATIVE AC/DOCETAXEL THE ADDITION OF DOCETAXEL TO AC ON PRIMARY TUMOR RESPONSE RESULTED IN:

- Equivalent rates of breast-conserving surgery and mastectomy
- Significantly increased clinical (65% to 40%) and pathological (25.6% to 13.7%) complete response rates
- A higher percentage of patients with histological negative axillary nodes (59.5% to 51.5%)
- Additional grade 4 toxicity (24% to 10%)

Note: 2,411 patients randomized, with an average time on study of approximately 40 months

Derived from NSABP Presentation, *2001 San Antonio Breast Cancer Symposium.* **Abstract 5.**

Neoadjuvant trastuzumab trial

In women with HER2-positive tumors — either 3+ on HercepTest™ or FISH-positive — we are conducting a single-institution neoadjuvant trastuzumab trial. All women receive four cycles of paclitaxel and four cycles of FEC with or without concurrent, weekly trastuzumab. We are employing very close cardiac monitoring. We thought epirubicin offered a lower risk of cardiac toxicity, and it was specifically chosen for that reason. Since we are only giving four cycles of FEC, the total cumulative dose of epirubicin and, hence, the risk of cardiac dysfunction should be very low.

Select publications

Adjuvant use of aromatase inhibitors

Pharmacokinetics of anastrozole and tamoxifen alone and in combination during adjuvant endocrine therapy for early breast cancer in postmenopausal women: A subprotocol of the "Arimidex® and Tamoxifen Alone or in Combination" (ATAC) trial. *Br J Cancer* 2001;85(3):317-324. **Abstract**

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Edited comments by Dr Robert

Phase II trial of trastuzumab in combination with carboplatin and paclitaxel for metastatic breast cancer

The pivotal trial by Slamon demonstrated the utility of using chemotherapy with trastuzumab. There was significant cardiotoxicity in those patients receiving AC plus trastuzumab, so that was not a regimen that could be developed further.

We designed a phase II trial that attempts to improve upon the trastuzumab / paclitaxel combination by adding in carboplatin. There is synergy between the platinum salts and trastuzumab, and clinical data from Edith Perez and the North Central Cancer Therapy Group demonstrated a 60% response rate from every-three-week paclitaxel and carboplatin. David Loesch from US Oncology obtained similar results with the same combination given on a different schedule.

Our study compares paclitaxel / trastuzumab to the combination of paclitaxel, trastuzumab and carboplatin. The target accrual is 205 patients, which is nearly completed. In terms of safety, preliminary data suggests that the two arms are comparable, with the exception of increased myelosuppression from adding in carboplatin.

Cardiotoxicity was not problematic, except for patients with a prior history of cardiac disease. We did not detect declines in left ventricular ejection fraction — relative to baseline — even in patients who received adjuvant anthracyclines.

GRADE 3/4 ADVERSE EVENTS IN A SAFETY STUDY COMPARING TRASTUZUMAB/PACLITAXEL (HT) AND TRASTUZUMAB/PACLITAXEL/CARBOPLATIN (HTC)

	HT (n=75)	HTC (n=76)
Hematologic	27 (36%)	60 (79%)
Neurologic	8 (11%)	12 (16%)
Gastrointestinal	3 (4%)	7 (9%)
Asthenia	5 (7%)	4 (5%)
Cardiovascular	6 (8%)	2 (3%)
Neutropenic fever	1 (1.3%)	4 (5%)

Derived from Robert NJ et al. *Breast Cancer Res Treat* 2001;Poster 529.

Pilot studies of trastuzumab with a taxane/platinum combination

Two pilot studies from the BCIRG and UCLA evaluated trastuzumab with a taxane/platinum regimen in HER2 FISH-positive patients with metastatic breast cancer. Improved response rates were demonstrated in the study utilizing carboplatin but not for cisplatin. Howard Burris at the Sarah Cannon Cancer Center gave trastuzumab up front to IHC 2/3+ HER2-positive patients with metastatic breast cancer. After eight weeks, patients with stable disease or progression were treated with paclitaxel and carboplatin with or without trastuzumab, and significant responses were seen.

Trastuzumab in combination with platinum agents

The combination of trastuzumab with platinum analogs was one of the initial strategies tested in the early development of trastuzumab. Although these studies demonstrated that the combination was well tolerated and showed antitumor efficacy, this strategy was not pursued further because cisplatin and carboplatin are not generally used in the treatment of breast cancer. Preclinical studies have demonstrated significant synergy between trastuzumab and both carboplatin and carboplatin plus docetaxel or paclitaxel. In addition, further studies have elucidated the probable mechanism for this synergy, which involves inhibition by trastuzumab of the repair of the DNA adducts formed due to cisplatin therapy.

EXCERPT FROM: Winer EP, Burstein HJ. *Oncology* 2001;61(suppl):50-57. **Abstract**

BCIRG 006 adjuvant trial

The pilot studies of trastuzumab combined with a taxane/platinum regimen were the impetus for the large adjuvant trial being conducted by the Breast Cancer International Research Group. It is a very well-designed study, which

evaluates three regimens in HER2-positive, node-positive and high-risk node-negative women with primary breast cancer. In two arms, patients receive doxorubicin and cyclophosphamide followed by docetaxel with or without trastuzumab. The third arm represents a departure from the standard approach of using anthracyclines in the adjuvant setting; patients will receive docetaxel, a platinum salt — carboplatin or cisplatin — and trastuzumab.

Phase III Randomized Study of Adjuvant Doxorubicin, Cyclophosphamide and Docetaxel with or without Trastuzumab (Herceptin) Versus Trastuzumab, Docetaxel and Either Carboplatin or Cisplatin in Women with HER2-neu-Expressing Node-Positive or High-Risk Node-Negative Operable Breast Cancer **Open Protocol**

Protocol IDs: AVENTIS-TAX-GMA-302, BCIRG-006, NCI-G01-1978, UAB-0106, UAB-F010326012, UCLA-010200601

Eligibility | Node-positive or high-risk node-negative, HER2-overexpressing (FISH-positive) breast cancer

ARM 1	AC x 4 → T x 4
ARM 2	AC x 4 → T x 4 + H (qw x 12 weeks) → H (qw x 40 weeks)
ARM 3	T + (cisplatin or carboplatin) x 6 + H (qw x 18 weeks) → H (qw x 34 weeks)

AC=doxorubicin/cyclophosphamide;
T=docetaxel; H=trastuzumab
ER/PR+ patients receive tamoxifen

STUDY CONTACT
Linnea Chap, Chair, Ph: 310-206-6144
Jonsson Comprehensive Cancer Center, UCLA

First-line therapy for HER2-positive metastatic breast cancer

I use the combination of paclitaxel and trastuzumab in HER2-positive patients with metastatic disease, but I am eagerly awaiting the results of our trial to determine if carboplatin adds to this regimen. Pilot studies conducted by Nabholtz and Slamon, which added carboplatin to trastuzumab/taxane, demonstrated prolongation in time to progression — 12 months in one trial and 17 months in the other. These compare very favorably to the seven months in time to progression seen in the trastuzumab pivotal trial. Three-drug combinations may turn out to be the preferred strategy for HER2-positive patients.

Trastuzumab monotherapy is also an attractive therapeutic approach. It is analogous to the use of sequential single-agent endocrine therapy for indolent metastatic disease. HER2-positive tumors are not necessarily always aggressive. Chuck Vogel demonstrated a very acceptable response rate and clinical benefit with single-agent trastuzumab. Howard Burris and his colleagues gave trastuzumab up front and used chemotherapy in those who failed to respond or progressed. This is a reasonable strategy and should be considered in appropriately chosen patients.

Duration of trastuzumab use

I continue trastuzumab as long as the patient has no evidence of cardiac problems. This strategy is unproven, but it is being evaluated in a trial conducted by MD Anderson. In this study, patients will be randomized to

COMPARISON OF PHASE II STUDIES WITH 6 CYCLES OF DOCETAXEL, PLATINUM AGENT AND TRASTUZUMAB (TCH) IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

	UCLA	BCIRG 101
Prior Adjuvant Therapy	67%	56%
anthracycline	44%	38%
taxane	11%	
Metastatic Disease		
2 or more organs involved	56%	70%
visceral	78%	76%
bone	41%	44%
lytic bone lesions	15%	
HER2 Status	FISH+	IHC 2+/3+
Platinum Agent	Carboplatin	Cisplatin
Clinical Response		
Complete Response (CR)	2/14 (14%)	3/34 (9%)
Partial Response (PR)	7/14 (50%)	23/34 (68%)
Overall Response (CR+PR)	9/14 (64%)	26/34 (76%)
Stable Disease (SD)	8/14 (57%)	4/34 (12%)

Slamon DJ et al. *Proc ASCO* 2001;**Abstract 193.** Pienkowski T et al. *Proc ASCO* 2001;**Abstract 2030.**

second-line therapy with vinorelbine or trastuzumab and vinorelbine. Typically, I use a trastuzumab/taxane combination for six months, then switch to single-agent trastuzumab. In the pivotal trial, most patients did not stay on chemotherapy indefinitely. If a patient fails trastuzumab and paclitaxel, then I will continue with single-agent trastuzumab and add in another synergistic agent, like vinorelbine.

Trastuzumab use after ACT adjuvant therapy

Women with HER2 overexpressing tumors who have failed prior ACT adjuvant therapy are a challenge to manage, and I consider when they failed that regimen and how they received the taxane. If they received a taxane on an every-three-week schedule, a weekly taxane can be used as salvage therapy, and I would be comfortable using trastuzumab with a taxane in that situation.

Clinical implications of the ATAC trial results

These data will have a huge impact on the clinical care of our patients. Disease-free survival and the toxicity profile were more favorable for anastrozole. There was less weight gain and fewer hot flashes with anastrozole but more arthralgias and concerns about bone density. This is definitely an option that we will need to discuss with our patients. If patients ask for advice, I will recommend anastrozole.

Switching patients from tamoxifen to anastrozole

For a woman who has received tamoxifen for two to three years, it is reasonable to continue that therapy. However, the ATAC trial results should be communicated to patients, and some will choose to switch to anastrozole. I would be comfortable with that decision. One cannot evaluate the ATAC trial in isolation. There are multiple trials that have demonstrated that aromatase inhibitors are superior to tamoxifen. The first lead in the adjuvant setting is a disease-free survival advantage; survival advantages are rarely seen in earlier analyses. At this time, the use of adjuvant anastrozole is analogous to the switch made in the late 1980s of offering chemotherapy to high-risk, node-negative patients when an advantage was demonstrated in disease-free survival. As the data were unfolding, some argued that it was necessary to see a survival advantage, but I believe that would have deprived patients of a successful intervention. Making decisions about when to adopt a new therapy is really the art of medicine interacting with science.

Interchangeability of aromatase inhibitors

Anastrozole was superior to tamoxifen in the ATAC trial. There are no data comparing the other aromatase inhibitors to tamoxifen in the adjuvant setting. Eventually letrozole and exemestane may also be shown to be better than tamoxifen as adjuvant therapy, but we do not have that data, so I would use anastrozole.

Adjuvant endocrine maneuvers in ER-positive premenopausal patients

In high-risk, ER-positive premenopausal women who continue to menstruate after chemotherapy, it is reasonable to use ovarian ablation/suppression. Nancy Davidson's update of the Intergroup 0101 trial demonstrated an advantage for adding goserelin and tamoxifen to CAF chemotherapy. Another strategy would be ovarian ablation/suppression plus an aromatase inhibitor. I have had excellent results with this combination in a few patients with metastatic disease, who continued menstruating and did not want chemotherapy. Interestingly, combination endocrine maneuvers have generally been unsuccessful. The newer aromatase inhibitors and fulvestrant have renewed interest in the idea that these agents may be additive with other endocrine interventions.

Phase III trial of fulvestrant versus anastrozole as second-line therapy in ER-positive postmenopausal patients

The North American trial suggested that fulvestrant may be superior to anastrozole as second-line therapy for metastatic disease, but overall, fulvestrant is at least comparable to anastrozole. We are fortunate to now have another useful endocrine intervention for our patients and another option to control their disease using a nonchemotherapy intervention. A higher dosage of fulvestrant may be even more effective, and this should be addressed in a clinical trial. The monthly intramuscular injection has not been problematic, particularly compared to chemotherapy. Fulvestrant is well tolerated, and I expect that patients will receive it favorably.

Select publications

Trastuzumab plus taxane and/or platinum salt regimens

Burris HA 3rd. **Docetaxel (Taxotere) plus trastuzumab (Herceptin) in breast cancer.** *Semin Oncol* 2001;28:38-44. **Abstract**

Burris III HA et al. **Phase II trial of Herceptin induction followed by combination therapy with paclitaxel and carboplatin: A Minnie Pearl Research Network trial.** *Breast Cancer Res Treat* 2000;Abstract 24.

Burstein HJ et al. **Preoperative trastuzumab (T) and paclitaxel (P) for HER2 overexpressing (HER2+) stage II/III breast cancer: Clinical, pathological and serological findings.** *Breast Cancer Res Treat* 2001;**Abstract 507.**

Crown JP. **The platinum agents: A role in breast cancer treatment?** *Semin Oncol* 2001;28(1 Suppl 3):28-37. **Abstract**

Dieras V et al. **Interaction between Herceptin and taxanes.** *Oncology* 2001;61 Suppl 2:43-9. **Abstract**

Loesch DM et al. **Weekly Taxol (T) and carboplatin (C) regimen in patients with advanced breast cancer: A phase II study.** *Breast Cancer Res Treat* 2000;Abstract 316.

Miller KD et al. **Gemcitabine, paclitaxel and trastuzumab in metastatic breast cancer.** *Oncology (Huntingt)* 2001;15:38-40. **Abstract**

Nabholtz JM et al. **Results of two open-label multicentre pilot phase II trials with Herceptin® in combination with docetaxel and platinum salts (cis- or carboplatin) (TCH) as therapy for advanced breast cancer in women overexpressing HER2.** *Breast Cancer Res Treat* 2000;**Abstract 327.**

Perez EA et al. **A phase II study of paclitaxel plus carboplatin as first-line chemotherapy for women with metastatic breast carcinoma.** *Cancer* 2000;88(1):124-31. **Abstract**

Pienkowski T et al. **Taxotere, cisplatin and Herceptin (TCH) in first-line HER2-positive metastatic breast cancer (MBC) patients, a phase II pilot study by the Breast Cancer International Research Group (BCIRG 101).** *Proc ASCO* 2001;**Abstract 2030.**

Robert NJ et al. **Toxicity profiles: A comparative study of Herceptin (trastuzumab) and Taxol (paclitaxel) versus Herceptin, Taxol and carboplatin in HER2-positive patients with advanced breast cancer.** *Breast Cancer Res Treat* 2001;**Abstract 529.**

Schueller JJS et al. **Pharmacokinetics (PK) of epirubicin (EPI) and docetaxel (DOCE) in combination with Herceptin (H) in breast cancer patients.** *Breast Cancer Res Treat* 2001;**Abstract 524.**

Sledge GW et al. **Pilot trial of Paclitaxel-Herceptin adjuvant therapy for early stage breast cancer (E2198).** *Breast Cancer Res Treat* 2001;**Abstract 4.**

Seidman AD et al. **Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification.** *J Clin Oncol* 2001;19:2587-95. **Abstract**

Slamon DJ et al. **Phase II pilot study of Herceptin combined with Taxotere and carboplatin (TCH) in metastatic breast cancer (MBC) patients overexpressing the HER2-neu proto-oncogene: A pilot study of the UCLA network.** *Proc ASCO* 2001;**Abstract 193.**

Slamon DJ et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001;344:783-92. **Abstract**

Slamon D, Pegram M. **Rationale for trastuzumab (Herceptin) in adjuvant breast cancer trials.** *Semin Oncol* 2001;28(1 Suppl 3):13-9. **Abstract**

Winer EP, Burstein HJ. **New combinations with Herceptin in metastatic breast cancer.** *Oncology* 2001;61 Suppl 2:50-7. **Abstract**

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals, LP
capecitabine	Xeloda®	Roche Laboratories, Inc.
cisplatin	Platinol AQ®	Bristol-Myers Squibb Company
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
clodronate	Not available in the United States	
cyclophosphamide	Cytoxan®, Neosar®	Bristol-Myers Squibb Company
docetaxel	Taxotere®	Aventis Pharmaceuticals
doxorubicin hydrochloride	Adriamycin®	Pharmacia Corporation
epirubicin	Ellence®	Pharmacia Corporation
exemestane phosphate	Aromasin®	Pharmacia Corporation
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals, LP
goserelin	Zoladex®	AstraZeneca Pharmaceuticals, LP
letrozole	Femara®	Novartis Pharmaceuticals
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pamidronate	Aredia®	Novartis Pharmaceuticals
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals, LP
trastuzumab	Herceptin®	Genentech, Inc.
vinorelbine tartrate	Navelbine®	Glaxo Wellcome, Inc.
ZD 1839	Iressa®	AstraZeneca Pharmaceuticals, LP
zoledronic acid	Zometa®	Novartis Pharmaceuticals

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Consultant: Genentech, Inc., AstraZeneca Pharmaceuticals, LP
Speakers' Bureau: AstraZeneca Pharmaceuticals, LP

Post-test

Questions ***(please circle answer)***

1. Which class of drugs is believed to have a promising role in offsetting potential anastrozole-related declines in bone density?

a. Bisphosphonates b. LHRH agonists c. SERMs d. Steroidal aromatase inhibitors

2. Fulvestrant is given:

a. Orally b. Transdermally c. Intravenously d. Intramuscularly

3. True/False: There are conclusive data showing the benefit of several different aromatase inhibitors in the adjuvant setting.

4. Fulvestrant is unique because it:

a. Upregulates estrogen receptors b. Downregulates estrogen receptors
c. Reduces estrogen to very low levels d. Is non-steroidal

5. True/False: Alopecia is not a common side effect of capecitabine.

6. Trastuzumab, in combination with which of the following agents, is indicated for HER2-overexpressing breast cancer patients who have not received chemotherapy for their metastatic disease.

a. Epirubicin b. Vinorelbine c. Paclitaxel d. Capecitabine

7. True/False: A Canadian study has shown that most patients prefer oral to IV chemotherapy if the efficacy and side effects are similar.

8. The side effects observed in the combination arm of the ATAC trial were:

a. Similar to anastrozole b. Similar to tamoxifen
c. Different than both anastrozole and tamoxifen d. Similar to both anastrozole and tamoxifen

9. In the HER2-positive patient with metastatic disease, trastuzumab is widely considered a:

a. First-line treatment b. Second-line treatment c. Third-line treatment d. Salvage treatment

10. True/False: Dose reduction is widely considered an effective strategy for managing capecitabine-associated toxicity.

Exam Answer Key: 1. A, 2. D, 3. False, 4. B, 5. True, 6. C, 7. True, 8. B, 9. A, 10. True

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Extent to which program activities met the identified objectives
Upon completion of this activity, participants should be able to:

- Describe the clinical implications of the ATAC trial results 5 4 3 2 1
- Review the side-effect profiles of anastrozole and tamoxifen 5 4 3 2 1
- Discuss the biology and mechanism of action of fulvestrant 5 4 3 2 1
- Discuss the role of capecitabine in the treatment of metastatic disease 5 4 3 2 1
- Review the design and rationale for the current MD Anderson neoadjuvant/adjuvant trial of paclitaxel versus docetaxel/capecitabine 5 4 3 2 1
- Describe potential strategies for treating the HER2-positive patient 5 4 3 2 1
- Review the preliminary results of the Phase II trial examining the combination of trastuzumab/carboplatin/paclitaxel 5 4 3 2 1

Overall effectiveness of the activity

Objectives were related to overall purpose/goal(s) of activity 5 4 3 2 1

Related to my practice needs 5 4 3 2 1

Will influence how I practice 5 4 3 2 1

Will help me improve patient care 5 4 3 2 1

Stimulated my intellectual curiosity 5 4 3 2 1

Overall quality of material 5 4 3 2 1

Overall, the activity met my expectations 5 4 3 2 1

Avoided commercial bias or influence 5 4 3 2 1

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 activity.

_____

_____

Degree:

❑ MD ❑ DO ❑ PharmD ❑ RN ❑ PA ❑ BS ❑ Other _____

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