Management of Breast Cancer in the Adjuvant and Metastatic Settings

750 Second Opinions:
Survey of Oncologists in Practice Regarding 10 Cases Presented by Their Colleagues

Interdisciplinary Perspective:
Survey Comparing Responses of Surgical and Medical Oncology Investigators and Surgeons and Medical Oncologists in Practice

Editor
Neil Love, MD

Patterns of Care in Medical Oncology

Sponsored by Research To Practice.
Copyright © 2009 Research To Practice.
This program is supported by educational grants from Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc and Sanofi-Aventis.

Last review date: February 2009
Release date: February 2009
Expiration date: February 2010
Estimated time to complete: 2.5 hours
Table of Contents

2  Continuing Medical Education Information
4  Editor’s Note: And now for something just a wee bit different!
5  Adjuvant Systemic Therapy
16  Treatment of Metastatic Disease
27  Perspectives on Systemic Treatment of Early Breast Cancer
31  Educational Assessment and Credit Form

PowerPoint files of the graphics contained in this document can be downloaded at www.ResearchToPractice.com/POC/Breast.
OVERVIEW OF ACTIVITY

It is important for general medical oncologists and surgeons to be aware of similarities and differences between their patterns of cancer care and those of other community practitioners and breast cancer clinical investigators. Additionally, the recognition that heterogeneity exists within the treating oncology community underscores the existence of clinical situations for which there may be suboptimal research evidence to support a single optimal approach.

This program focuses on the self-described practice patterns of randomly selected medical oncologists and general surgeons in a variety of key clinical scenarios in breast cancer. Also included are clinical investigator commentary and references addressing these topics. This CME program will provide oncologists and general surgeons information on national cancer care and those of other community practitioners and breast cancer clinical investigators.

LEARNING OBJECTIVES

• Compare treatment strategies utilized by community oncologists, general surgeons and cancer clinical investigators in the primary, adjuvant and metastatic settings, and apply this information to the routine management of breast cancer.

• Evaluate clinical issues for which relative agreement and heterogeneity exist in patterns of breast cancer care, and make treatment decisions considering this information.

• Counsel patients with breast cancer about the benefits and risks of multiple acceptable treatment options when they exist.

• Recognize the rate at which practice-changing clinical research impacts physician decision-making, and explain how this affects oncology patient access to standard and novel therapies.

• Recall the design and eligibility criteria for ongoing breast cancer clinical trials, and consider appropriate patients for study participation.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 2.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This monograph is one issue of a CME series activity. To receive credit for this activity, the participant should read the monograph and complete the Educational Assessment and Credit Form located in the back of this book or on our website at www.ResearchToPractice.com/PDA/Breast.

COMMERCIAL SUPPORT

This program is supported by educational grants from Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc and Sanofi-Aventis.

PHARMACEUTICAL AGENTS DISCUSSED IN THIS PROGRAM

This educational activity includes discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

CME DISCLOSURES FOR COMMUNITY ONCOLOGISTS WHO PROVIDED CASES

Drs Bobrow, Hoffman, Levy and Schwartz had no financial interests or affiliations to disclose.

Dr Hart — Speakers Bureau: GlaxoSmithKline.

Dr Kanner — Advisory Committee: AstraZeneca Pharmaceuticals LP, Celgene Corporation, Eisai Inc, Millennium Pharmaceuticals Inc.

Dr Schwarzberg — Advisory Committee: Pfizer Inc; Speakers Bureau: Novartis Pharmaceuticals Corporation, Pfizer Inc.

CME DISCLOSURES FOR QUOTED FACULTY

Drs Dixon and Winer had no real or apparent conflicts of interest to disclose. The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: Dr Burris — Consulting Agreements: Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology, GlaxoSmithKline, ImClone Systems Incorporated, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc. Prof Crown — Speakers Bureau: GlaxoSmithKline, Pfizer Inc, Sanofi-Aventis. Dr Gradishar — Advisory Committee: Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eisai Inc, Genentech BioOncology.

CONTINUED ON PAGE 3

ABOUT THESE SURVEYS

The Second Opinion survey was completed in November 2008 by 75 US-based community-based medical oncologists.

The Perspectives on Systemic Treatment of Early Breast Cancer survey was conducted in two phases. Phase I was completed in February 2008 by 100 general surgeons and 28 surgical clinical investigators who practice in the United States.

Phase II of the survey was completed in March 2008 by 100 community-based medical oncologists and 43 oncologists who specialize in breast cancer management in the United States.

Portions of the data obtained from the February and March 2008 surveys have been previously published by Research To Practice. To obtain the related programs, please visit www.ResearchToPractice.com.

EDITOR — Neil Love: Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Biogen Idec, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Eisai Inc, Eli Lilly and Company, Genentech BioOncology, Genomic Health Inc, Genzyme Corporation, GlaxoSmithKline, ImClone Systems Incorporated, Merck and Company Inc, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Ortho Biotech Products LP, OSI Oncology, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis, Synta Pharmaceuticals Corp and Wyeth.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.
Editor’s Note: And now for something just a wee bit different!

This issue of Patterns of Care is being mailed at the same time as a sibling education piece, “Second Opinion,” a four-CD audio extravaganza that includes highlights of two satellite symposia our CME group held in December 2008 at the San Antonio Breast Cancer Symposium.

At the center of these complimentary educational activities are 12 cases from the clinics of medical oncologists practicing in a community setting. These were chosen over dozens of others because they typify the most challenging situations medical oncologists currently encounter with regard to breast cancer treatment.

On these pages you will see how 75 randomly selected general oncologists would manage these cases, and in the supporting text, breast cancer clinical investigators weigh in on these patients and the clinical scenarios.

Similarly, on the four-plus-hour monster audio program (good for a slow drive on a Sunday afternoon or 10 short drives to work!) these cases and the issues surrounding them are discussed and rediscussed by the learned faculty members who participated in our recent symposia.

What these integrated activities do besides delivering some thought-provoking and insightful perspectives is provide a snapshot of the relative homogeneity in how US-based oncologists think things through when caring for people with breast cancer at tertiary meccas or down the street.

Another unique aspect of this issue is that we have included a “tasting menu” of data collected from surgical colleagues, and presented during a satellite symposium at the 2008 American Society of Breast Surgeons annual meeting in New York. The responses of the breast and general surgeons surveyed are shown in comparison to those of medical oncologists, and while there certainly are discernable differences in how these specialists respond to questions about systemic therapy, the discrepancies are to my eyes not very dramatic.

This suggests that many or most surgeons are following the lead of surgical investigator legend Dr Bernard Fisher who believes that breast cancer is a systemic disease and that physicians caring for these patients must give proper credence to this essential therapeutic approach.

There actually is a theme to this madness. Clinical research information and investigator perspectives are being rapidly and effectively transmitted to physicians caring for people with breast cancer in community practice. That’s a good thing. Now we must provide them much better therapeutic tools to deal with this disease.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
February 18, 2009


FACULTY: (Row 3, left to right) Mark D Pegram, MD; J Michael Dixon, MD; Pat W Whitworth Jr, MD; Peter M Ravdin, MD, PhD


FACULTY: (Counterclockwise from top left) Sandra M Swain, MD; Kathy D Miller, MD; Eleftherios P Mamounas, MD, MPH; John Crown, MD; Daniel F Hayes, MD; William J Gradishar, MD; Howard A Burris III, MD; Julie R Gralow, MD; Eric P Winer, MD; George W Sledge Jr, MD; Joyce O’Shaughnessy, MD; Peter M Ravdin, MD, PhD


FACULTY: (Row 3, left to right) Mark D Pegram, MD; J Michael Dixon, MD; Pat W Whitworth Jr, MD; Peter M Ravdin, MD, PhD
**Case 1:** A 76-year-old woman is diagnosed with a 0.8-cm, ER/PR-positive, HER2-negative, moderately differentiated infiltrating ductal carcinoma (IDC). The patient has 1 positive sentinel node and 1 positive axillary node of 15 excised nodes.

— Samuel N Bobrow, MD
New Haven, Connecticut

**Would you recommend the Oncotype DX® assay for this patient?**

<table>
<thead>
<tr>
<th>% responding yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

**Which endocrine therapy, if any, would you most likely recommend for this patient?**

- Anastrozole: 60%
- Letrozole: 31%
- Exemestane: 2%
- Tamoxifen: 7%

**Which chemotherapy regimen, if any, would you likely recommend for this patient?**

- TC: 60%
- AC or AC → T: 11%
- CMF: 7%
- Would not recommend chemo: 22%

**Comment from the Treating Physician**

**Samuel N Bobrow, MD:** This patient would consider chemotherapy. If I had felt strongly that she needed it, I probably could have convinced her to receive chemotherapy. However, she was not happy about the idea. We sent the Oncotype DX, and the Recurrence Score® was 5 so we were comfortable using radiation therapy followed by an aromatase inhibitor.

**Select Commentary from Interviews Conducted at SABCS 2008**

**George W Sledge Jr, MD:** I believe it’s reasonable to consider the Oncotype DX assay for this patient. We certainly have evidence suggesting that patients with low Recurrence Scores are likely not to receive much benefit from chemotherapy. It strikes me as relatively unlikely that the biology of breast cancer changes dramatically from lymph node-negative to one or two positive nodes.

My baseline in this case would be hormonal therapy, and I would not be inclined to recommend chemotherapy unless I had striking evidence that the patient might benefit. While we don’t know how Oncotype DX data break down by age, we certainly do know of older women who are healthy, have no comorbidities and have sufficiently aggressive cancer that one might expect some benefit from chemotherapy.

**Howard A Burris III, MD:** I have not begun to use Oncotype DX for patients with node-positive breast cancer. I’m interested in the data and believe they will become more relevant, but right now if the patient is committed to receiving chemotherapy, then I do not use the assay. Even for older patients, I’ve been so comfortable with TC — that’s my new CMF — that I don’t order the Oncotype, although maybe it would tell me I don’t need chemotherapy for some of those patients.

**Julie R Gralow, MD:** Five is a partic-
Adjuvant Systemic Therapy (Continued)

**CASE 1a (continued): The patient had an Oncotype DX assay performed that revealed a Recurrence Score of 5.**

What would be your most likely treatment recommendation for this patient?

- Hormonal therapy alone: 57%
- TC → hormonal therapy: 24%
- AC → hormonal therapy: 7%
- CMF → hormonal therapy: 7%
- Other chemotherapy → hormonal therapy: 5%

Have you ordered the Oncotype DX assay for a patient with node-positive breast cancer?

% responding yes: 47%

If yes, for how many patients with node-positive breast cancer have you ordered the Oncotype DX assay?

Mean: 4

What is the approximate age of the oldest patient with breast cancer that you have treated with adjuvant chemotherapy?

- 60-69: 5%
- 70-79: 49%
- 80-89: 43%
- ≥90: 3%
CASE 2: A 67-year-old woman was diagnosed with a 2.5-cm, node-negative, ER/PR-positive, HER2-negative IDC in 2003. Bone mineral density (BMD) was normal. The patient has been treated with anastrozole since that time and has tolerated this treatment without side effects or bone loss.

— Kenneth R Hoffman, MD, MPH
Teaneck, New Jersey

Would you continue the anastrozole beyond the 5-year point for this patient?

% responding yes

0 10 20 30 40 50 60 70 80 90

27%

When was the last time you faced the decision of whether to continue an AI at 5 years?

1-3 months ago

4-6 months ago

>6 months ago

90%

8%

2%

n = 62

Was the tumor node-negative or node-positive?

Node-negative

Node-positive

40%

60%

Did the patient continue the AI?

% responding yes

Node-negative

Node-positive

13%

53%

Select Commentary from Interviews Conducted at SABCS 2008

PETER M RAVDIN, MD, PHD: One of the issues that shades our thinking is how much residual risk of disease recurrence the patient has after five years of adjuvant endocrine therapy. For a patient with a 2.5-cm, node-negative breast tumor, I estimate that she has approximately a two percent per year risk of developing recurrence.

DR GRALOW: I probably wouldn’t continue an aromatase inhibitor for this patient beyond five years, outside of a clinical trial. On the other hand, if her disease were node-positive, I probably would consider doing so. It’s clear that patients with ER-positive breast cancer have a somewhat lower risk of relapse in the first five years compared to those with ER-negative disease. However, they also have a small but real rate of relapse that goes on forever, and they may benefit from prolonged endocrine therapy.

The NCI Canada MA17 trial showed a survival benefit for patients with node-positive disease who received five years of letrozole after five years of tamoxifen. We also know that continued aromatase inhibitor treatment will have some impact on bone and, whether or not it causes a statistical increase in cardiovascular events, a subpopulation certainly exists in whom the lipids are affected by it.

We now have a couple of ongoing studies evaluating whether an additional five years of an aromatase inhibitor is beneficial after patients have already completed five years, whether or not they

COMMENT FROM THE TREATING PHYSICIAN

KENNETH R HOFFMAN, MD, MPH:
This is an active patient who had no problems with arthralgias or bone loss while on anastrozole. The decision came down to what the patient wanted, and she wanted to stop therapy. She felt that every morning when she took her pill, it reminded her of her cancer and she wanted to be cancer free in her mind.
ADJUVANT SYSTEMIC THERAPY

As for side effects, approximately 75 percent of my patients are able to remain on aromatase inhibitor therapy for five years. Most of them can tolerate the hot flashes, but at least 20 percent quit because of significant arthralgias and myalgias.

JOYCE O’SHAUGHNESSY, MD: For patients at lower risk like this, I have not been continuing an aromatase inhibitor beyond five years. In my practice, patients either want to stay on therapy or they cannot wait to stop and they are counting the days. The patient’s desire is influenced by two variables: whether they perceive themselves to be at high risk and whether they have found the treatment to be tolerable.

I find that if patients perceive themselves to be at high risk, they want to continue treatment. If I believe the tumor is indolent biologically, strongly ER driven, but still the patient wishes to continue and it’s not bothering her, I don’t object. However, patients with node-negative disease are generally anxious to quit therapy.

As for tolerability, I would estimate that two thirds of my patients on an aromatase inhibitor experience musculoskeletal symptoms, but 85 to 90 percent of the patients who return to see me in the clinic remain on therapy for the full five years without major side effects.

The ATAC data have shown that approximately 50 percent of patients with these complaints improve within a year or so. I check the vitamin D levels to ensure they are not too low, and I recommend simple practices like stretching to ameliorate the symptoms.

DR SLEDGE: In our institution, we are conducting a pharmacogenomics study of aromatase inhibitors for early-stage breast cancer. If a patient has a significant level of arthralgias, she is referred to a rheumatologist. These specialists are interested in evaluating exercise interventions, including stretching and walking. Although we as clinicians tell our patients to do these things, rheumatologists deal with these issues daily, and we have found their interventions to be of value to many of our patients.
**CASE 3**: A 76-year-old woman who underwent a modified mastectomy for a 6-cm, Grade III, ER/PR-positive, HER2-positive (FISH 3.4) IDC. The tumor was staged as T4b and extended to the skin with ulceration and extensive dermal involvement.

— Isaac Levy, MD
Pembroke Pines, Florida

Along with trastuzumab, which chemotherapy, if any, would you recommend for this patient?

**FIGURE 6**

**FIGURE 7**

**CASE 3 follow-up**: The patient received TCH (docetaxel/carboplatin/trastuzumab) but developed an abscess related to perforated diverticuli during the sixth cycle, which required surgical intervention. Based on input from the surgeon and patient, systemic therapy was withheld until the abdominal process cleared, which took 6 months.

**COMMENT FROM THE TREATING PHYSICIAN**

**ISAAC LEVY, MD**: The patient is pretty much recovered from surgery and back on her feet, but six months have elapsed since she last received trastuzumab. Her family did not want her to resume therapy earlier, since she developed the abscess while on treatment. A recent MUGA scan revealed good cardiac function and ejection fraction. The question now is how to treat the patient with regard to trastuzumab. What is the optimal duration of treatment? How much maintenance trastuzumab is adequate in a case such as this one?

**KATHY D MILLER, MD**: I struggle with the issue of anthracyclines because although I believe that the BCIRG 006 trial data are compelling, the study does not yet have enough events to directly compare the ACTH arm to the TCH arm. However, they look similar and it seems unlikely to me that we will see a great enough improvement in efficacy with the anthracycline to counterbalance the clear increase in acute and potential long-term toxicity. Thus, in practice I would administer TCH and I’m quite comfortable with that. In fact, outside of the protocol setting, I haven’t used an anthracycline in a HER2-positive setting for the past 12 to 18 months.

**PROFESSOR JOHN CROWN, MD**: I would be nervous about treating any patient who has potentially curable cancer with the combination of trastuzumab and an anthracycline.

I don’t believe a strong argument for it exists right now. In general, the anthracycline-induced cardiotoxicity we see is what stays with the patient. Everything we know about combining an anthracycline and trastuzumab suggests trastuzumab makes the qualitative anthracycline lesion more frequent and more severe. In our study, patients who
Adjuvant Systemic Therapy (Continued)

FIGURE 8

Along with trastuzumab, which endocrine therapy, if any, would you recommend for this patient?

DANIEL F HAYES, MD: This patient’s prognosis is poor, yet the disease is still potentially curable. The CIRG data have not yet been published in a peer-review journal, and we have a wealth of data with AC followed by T with trastuzumab (H). In my practice, assuming this patient is in good shape and has a good heart to begin with, I would treat her with AC followed by T and H. I’m using anthracyclines for patients with node-positive disease almost routinely.

I do believe TCH is an effective regimen, and I’m using it mostly for patients with a better prognosis, such as node-negative cases. For those patients, I’m concerned about long-term heart failure because they have a better chance of living longer no matter what we do.

SANDRA M SWAIN, MD: Clearly anthracyclines damage the heart. That’s a big issue, but fortunately we now have other regimens that are effective. If we examine the data from the adjuvant trastuzumab trials for patients who received benefit from trastuzumab, those on TCH had few heart problems. In fact, their incidence was quite similar, if not the same, in the control group. Also, in the HERA trial, in which trastuzumab was administered after chemotherapy, much less heart failure occurred.

ELEFTHERIOS P MAMOUNAS, MD, MPH: Obviously, if we delay the start of chemotherapy the benefit decreases, but we don’t have a lot of data in this type of scenario.

I understand all the issues regarding the perforated diverticulitis in this case, but as long as it was resolved, I believe the trastuzumab could have been restarted a little earlier, maybe within a couple of months. I have no reason to believe it would cause neutropenia. However, that’s not the question. Six months have passed, and I believe at this point the most logical approach is to treat her. We know from the HERA trial that sequential trastuzumab after chemotherapy was still effective, so I would put her on trastuzumab for at least another six months.

DR SWAIN: I agree that we don’t have a lot of data in a situation like this, but we do know that trastuzumab stays around a long time — five half-lives means that it would still be present several months after it was discontinued. I also agree that I would have restarted it earlier, if the family had agreed to it. Another issue is the patient’s age. The number of deaths from breast cancer in women older than age 60 is a significant problem, so I’m curious about the viewpoint.

Right now we don’t have a good answer to the question, “Should we continue the trastuzumab for a year?” The FinHer trial — using only nine weeks of trastuzumab — had a small number of patients, but it is being followed by the SOLD study in which nine weeks is compared to about a year of trastuzumab.

The HERA trial evaluates one versus two years of trastuzumab, and a French trial is comparing six months to one year. These trials will eventually provide us with more data on the optimal duration of trastuzumab to help us in cases like this. A final point about this case is that it’s interesting that a medical oncologist didn’t consult with this patient before she went to surgery, because clearly most of us would have recommended neoadjuvant therapy for this patient with T4B breast cancer.

A few clinical trials address the issue of neoadjuvant chemotherapy/trastuzumab for patients with HER2-positive breast cancer. Aman Buzdar published data from a randomized clinical trial, which demonstrated a high pathologic complete response rate — 65 percent — for those patients who received a trastuzumab-containing chemotherapy regimen.

More recently, Dr. Gianni presented an update on the NOAH trial for patients with locally advanced, HER2-positive breast cancer who received neoadjuvant trastuzumab or not with a concurrent anthracycline-containing regimen. The pathologic complete response rate was 43 percent for those who received trastuzumab and 23 percent for those who did not. We never see such high pathologic complete response rates with standard chemotherapy among patients with HER2-negative disease.
**CASE 4:** A 37-year-old woman is diagnosed with a 0.4-cm, moderately differentiated infiltrating ductal carcinoma. The tumor is ER/PR-negative and HER2-positive by FISH.

— Samuel N Bobrow, MD
New Haven, Connecticut

**Which systemic therapy, if any, would you recommend for this patient?**

- TCH (doce/carbo/trast) 37%
- Doce/cyclophos/trast 16%
- Anthracycline regimen 4%
- Taxane/trast 4%
- No systemic therapy 39%
- Other 4%

**When was the last time you faced the following decision: Whether to administer adjuvant therapy to a patient with a node-negative, HER2-positive tumor smaller than 1 centimeter?**

- 1-3 months ago 55%
- 4-6 months ago 29%
- 7-9 months ago 7%
- 10-12 months ago 9%

**What was the approximate age of your patient?**

- <35 2%
- 35-49 53%
- 50-65 38%
- >65 7%

**Comment from the treating physician**

**SAMUEL N BOBROW, MD:** The woman is very anxious and wants to do everything that can be done. Would you use trastuzumab in this patient? If so, would you give it alone or with a chemotherapy regimen? I never use trastuzumab as monotherapy.

**Select Commentary from Interviews Conducted at SABCS 2008**

**DR GRALOW:** For this patient, endocrine therapy is not an option, and if I administer trastuzumab I don’t generally use it as monotherapy because I believe it has real synergy with chemotherapy. This woman’s age is also a consideration. She is young, and that worries me because she has many years ahead in which to relapse.

In making a treatment decision, one must consider both the biology and stage of her breast cancer. This tumor is at low stage, but the biology is bad, so I would offer her the combination of chemotherapy and trastuzumab. If she were eligible for our paclitaxel/trastuzumab trial, my preference would be to enroll her on that to avoid cardiotoxicity. However, I would also feel justified being more aggressive.

**DR SLEDGE:** We don’t have data from a prospective randomized trial in this area, and when no data exist, everyone is right. This is a real concern. A similar dilemma occurs when a patient has a small, ER-positive, HER2-positive tumor. Do you treat that patient with only endocrine therapy?

In these cases we need to tell patients that we don’t have any data. The data we do have across a variety of nodal statuses and sizes show us that trastuzumab is beneficial. However, with a smaller tumor the recurrence risk certainly could be less.

I don’t know what the patient’s risk of cancer relapse is, but if the cancer did recur, it would probably be within the next five years. Our experience with HER2-positive breast cancer tells us that if it recurs, it often recurs early. My suspi-
However, I haven’t seen many patients with 13 positive nodes, either.

**DR O’SHAUGHNESSY:** In my practice, I would probably treat this patient with Steve Jones’s TC regimen, which is docetaxel/cyclophosphamide, and trastuzumab.

We don’t have good data with tumors only four millimeters in size. However, being conservative in our estimates, we’d say she has about a six to seven percent risk of recurrence. That’s based on the rule of thumb that the recurrence risk is approximately 12 percent per centimeter of tumor, multiplied by 1.5 to estimate the relative risk with HER2.

That may be underestimating because we do have a few small series that indicate the risk of recurrence with even T1B lesions can be as high as 20 percent.

I would review the recurrence risk with the patient and tell her that chemotherapy will decrease that by half in her age group with ER-negative disease and trastuzumab will decrease it by another 50 percent. The absolute benefit comes out at approximately five percent, and I’m happy to treat patients for a benefit of five percent. That’s how I rationalize treating HER2-positive lesions that are so small.

My record is with a patient I’m treating now for a HER2-positive, ER/PR-negative, 3-mm invasive breast carcinoma. She is a healthy woman in her mid fifties with a normal LVEF and she’s normotensive. We enrolled her on a clinical trial of docetaxel/cyclophosphamide for four cycles with weekly trastuzumab, followed by trastuzumab every three weeks to complete one year of anti-HER2 therapy (Figure 11).

In this trial, we are using Steve Jones’s TC regimen, with cyclophosphamide rather than carboplatin, because it’s been proven beneficial in a mixed HER2-positive and HER2-negative population with only four cycles. I also find cyclophosphamide to be better tolerated than carboplatin, cycle for cycle.

With cyclophosphamide, we see a shorter duration of fatigue and avoid the risk of carboplatin anaphylaxis.

---

**FIGURE 10**

*Did your patient who presented with a subcentimeter, HER2-positive tumor receive both trastuzumab and chemotherapy?*

| % responding yes | 62% |

**FIGURE 11**

*Phase II trial of adjuvant docetaxel/cyclophosphamide with trastuzumab in HER2-positive early breast cancer*

Protocol IDs: 11270, NCT00493649
Accrual: 263 (Open)

<table>
<thead>
<tr>
<th>Eligibility</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Operable, invasive breast carcinoma</td>
<td></td>
</tr>
<tr>
<td>HER2-positive (IHC 3+ or FISH positive)</td>
<td></td>
</tr>
<tr>
<td>Stage I, IIA, IIB, or IIIA T1-3N1-3M0 disease</td>
<td></td>
</tr>
<tr>
<td>1 to 3 positive nodes</td>
<td></td>
</tr>
</tbody>
</table>

**Preliminary toxicity data: Grade III or IV toxicity in more than 5 percent of patients**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>128</td>
<td>49.4%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>41</td>
<td>15.8%</td>
</tr>
<tr>
<td>Febrile neutropenia*</td>
<td>15</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

* Only 6 patients (2%) received prophylactic WBC growth factors with cycle 1 of treatment.
Note: 145 patients (55%) received WBC growth factors at some time during the study.

**SOURCE:** Jones SE et al. San Antonio Breast Cancer Symposium 2008;Poster 2111.
CASE 5: A 41-year-old woman with Type 1 diabetes for 36 years who recently underwent laser therapy to her retinas is diagnosed with a 1.8-cm, triple-negative IDC.
— Kenneth R Hoffman, MD, MPH
Teaneck, New Jersey

Which chemotherapy regimen, if any, would you generally recommend for this patient?

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>56%</td>
</tr>
<tr>
<td>Dose-dense AC → paclitaxel</td>
<td>10%</td>
</tr>
<tr>
<td>AC → nab paclitaxel qwk</td>
<td>10%</td>
</tr>
<tr>
<td>AC</td>
<td>8%</td>
</tr>
<tr>
<td>AC → paclitaxel qwk</td>
<td>7%</td>
</tr>
<tr>
<td>TAC</td>
<td>3%</td>
</tr>
<tr>
<td>FEC</td>
<td>3%</td>
</tr>
<tr>
<td>Would not recommend chemo</td>
<td>3%</td>
</tr>
</tbody>
</table>

What would you recommend for the same patient, but with 3 positive nodes?

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-dense AC → paclitaxel</td>
<td>25%</td>
</tr>
<tr>
<td>TC</td>
<td>21%</td>
</tr>
<tr>
<td>TAC</td>
<td>21%</td>
</tr>
<tr>
<td>AC → paclitaxel qwk</td>
<td>20%</td>
</tr>
<tr>
<td>AC → nab paclitaxel qwk</td>
<td>7%</td>
</tr>
<tr>
<td>AC</td>
<td>6%</td>
</tr>
</tbody>
</table>
followed by a taxane because of her increased recurrence risk. I would probably try paclitaxel initially and monitor how much neuropathy she experienced after the first cycle.

DR SLEDGE: When patients are brittle and diabetic, I worry about how the drugs I choose to treat their cancer with may harm them.

During my residency, when we stepped outside a patient’s room, one physician would always ask me, “What have we done to this patient?” Not what have we done for this patient, but what have we done to this patient, and this diabetic is a patient whom it’s easy to do something to.

For example, administering a taxane-based regimen that would require a fair amount of steroids could have disastrous consequences if one were not careful about managing her diabetes. Older medical oncologists are not trained diabetologists, so that’s certainly one issue. Treating a diabetic with nab paclitaxel allows us to avoid steroids, and I have used that approach.

The other concern is peripheral neuropathy. Considering the side effects of taxane-based therapies and platinating agents, it is an issue for this patient.

It’s important to discuss side effects with patients before they start their adjuvant therapy and to be open and honest. In the vast majority of cases, our patients are frightened of breast cancer and they will do anything they can to not die from the disease. However, if we do not discuss these toxicities and they experience them, then they have every right to be unhappy with us.

If this patient had positive nodes, I would consider AC followed by nab paclitaxel. Since this case is node-negative, certainly a TC-type regimen is an appropriate alternative.

Although we have no data to support it, one could consider a nab paclitaxel/cyclophosphamide regimen in this setting. Unfortunately, our clinical trials are designed to observe the average patient and not the exceptions.

DR MILLER: This case is challenging because with her comorbidities we need to know more about the severity of her diabetes and its complications.

The patient has at least a moderate risk of recurrence, with approximately a 17 percent risk of death. She is also someone who would derive substantial absolute benefit from chemotherapy with either second- or third-generation regimens, so she needs to hear about chemotherapy. However, it must be a longer discussion than most because of her longstanding Type 1 diabetes. We also need to know more about any preexisting neuropathy and her baseline cardiac function.

It would be reasonable to worry about asymptomatic baseline cardiac dysfunction in a patient with her diabetic history. Even if her ejection fraction is normal, the evidence is fairly good that she is at greater risk of cardiac toxicity or dysfunction for the rest of her life, and anthracyclines would increase that risk.

To complicate matters further, this patient has triple-negative disease, and some literature suggests that, although less in the clinic at this point, anthracyclines and taxanes might be less effective than some chemotherapy regimens we don’t commonly consider. Few clinical data support that contention — and none in the adjuvant setting.

We do know from the ECOG-E2100 trial, evaluating first-line paclitaxel with or without bevacizumab for metastatic breast cancer, that patients with triple-negative disease had a hazard ratio for benefit of 0.56, which was one of the best subgroups examined in that trial.

My recommendation for this patient would be TC, although in general I don’t use that regimen. Although I’m not certain TC is more effective than AC, I’m not concerned that it is worse. As far as I know, the regimens that have been compared to AC have been either equivalent or more effective, and they had some toxicity benefits.

On the TC regimen, the patient will have less total exposure to steroids and less risk of neuropathy than with some of the other taxane regimens. It also avoids the potential complicating issues of anthracyclines and cardiac function.

SELECT PUBLICATIONS

CASE 1


Ingle JN et al. Aromatase inhibitors versus tamoxifen as adjuvant therapy for postmenopausal women with estrogen receptor positive breast cancer: Meta-analyses of randomized trials of monotherapy and switching strategies. SABCS 2008; Abstract 12.

Jones SE et al. Extended follow-up and analysis by age of the US Oncology Adjuvant trial 9735: Docetaxel/cyclophosphamide is associated with an overall survival benefit compared to doxorubicin/cyclophosphamide and is well-tolerated in women 65 or older. SABCS 2007; Abstract 12.


CASE 2


CASE 3


Jones SE et al. Preliminary toxicity results of a phase II trial of adjuvant docetaxel/cyclophosphamide plus trastuzumab in HER2+ early stage breast cancer patients. SABCS 2008; Abstract 2111.


Slamon D et al. BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel/cyclophosphamide (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients. SABCS 2006; Abstract 52.


Norris B et al. Poor 10 yr breast cancer specific survival (BCSS) and relapse free survival (RFS) for HER-2 positive T1pN0 tumors. SABCS 2006; Abstract 2031.

Rakshit R et al. Significant increased recurrence rates among breast cancer patients with HER2-positive, T1aN0M0 tumors. SABCS 2008; Abstract 701.

Trow SM et al. Poor survival outcomes in HER2 positive breast cancer patients with low grade, node negative tumours. Implications for trastuzumab therapy? SABCS 2008; Abstract 702.


CASE 5

Barlett JMS et al. Chromosome 17 polysomy (Ch17) as a predictor of anthracycline response: Emerging evidence from the UK NEAT adjuvant breast cancer trial. SABCS 2008; Abstract 45.


Finn RS et al. Phase II trial of dasatinib in triple-negative breast cancer: Results of study CA180599. SABCS 2008; Abstract 3118.


Koster F et al. Triple-negative breast cancer express receptors for growth hormone-releasing hormone (GHRH) and respond to GHRH antagonists with growth inhibition. Breast Cancer Res Treat 2008; [Epub ahead of print]. Abstract


ADJUVANT SYSTEMIC THERAPY

ISSUE 2
**CASE 6:** A 38-year-old premenopausal woman is diagnosed with a 2-cm, Grade III, ER/PR-positive, HER2-positive IDBC. MRI revealed a 1.8-cm nodule in the left lobe of the liver, and biopsy confirmed metastatic disease. The remainder of this patient’s workup is negative.

— Abraham B Schwarzberg, MD
West Palm Beach, Florida

**Which initial treatment strategy would you most likely recommend for this patient?**

- Trastuzumab and chemotherapy: 47%
- Trastuzumab/chemotherapy → endocrine therapy: 40%
- Trastuzumab and endocrine therapy: 4%
- Removal of the breast lesion and hepatic lesion: 4%
- Endocrine therapy alone: 3%
- Trastuzumab alone: 1%
- Removal of the breast lesion (+/- snb): 1%

**Which endocrine therapy recommendation would you most likely make for this patient?**

- Tamoxifen alone: 48%
- Ovarian suppression/ablation (OSA) with tamoxifen: 32%
- OSA with an AI: 17%
- OSA alone: 3%

**COMMENT FROM THE TREATING PHYSICIAN**

ABRAHAM B SCHWARZBERG, MD:
I treated her for approximately six months with paclitaxel/trastuzumab and she had a complete clinical response, but she developed severe nail problems, pain and fatigue. At that point, we decided to take a break to address local control of her primary tumor, and she underwent a lumpectomy with axillary dissection. She was premenopausal, so we also removed her ovaries at the same time, as a hormonal therapeutic maneuver, and we started tamoxifen.

The question then became, what do we do about the liver metastasis? In the treatment of metastatic disease there is no clear indication of the correct course of action. The decision was made to rebiopsy the liver nodule and perform radiofrequency ablation (RFA). No disease was evident during the biopsy or RFA. Necrotic tissue was found but nothing was viable, and she tolerated the procedure fine. She continues to take tamoxifen.

DR HAYES: A number of philosophical approaches to this patient are available. One is to acknowledge that she has metastases, and the treatment is palliation. Therefore, one wants to choose a treatment most likely to work with the fewest side effects to keep her feeling normal as long as possible.

I tell my patients, “The bad news is you have metastatic breast cancer, and we will probably not cure you. The good news is you have metastatic breast cancer, and we have many treatment options now.”

Many of those options are interchangeable, and the key is to work with the patient and her family to find the best treatments for that patient. There’s no right or wrong there.
DR MILLER: From the long-term follow-up series at MD Anderson, we know that a small group of patients are potentially cured of their metastatic disease, or, at least, long-term survivors have been followed for up to 10 years without evidence of recurrence or more cancer.

We don’t know a lot about who those women are, but we do know who they are not. They are not women who are symptomatic from their metastatic disease or have multiple, bulky sites of metastatic disease. They are not women who don’t have a complete response to their systemic therapy. These women were predominantly treated with anthracycline-based regimens and hormone therapy, if that would have been appropriate for their disease. None of them were assessed for HER2 or treated with HER2-targeted therapies.

I tell these patients that in general metastatic disease is not curable, but some exceptions occur. In a younger patient who has limited, asymptomatic metastatic disease, it would be reasonable to begin with the assumption that a few women are long-term survivors, and a key component would be a complete response to initial systemic therapy. Therefore, we would start with an aggressive plan that would offer her the best chance of achieving a complete response, and then the rest of our decisions would follow from how well she responded.

For this woman with a HER2-positive tumor, I would start with something like the TCH regimen. She would be eligible for ECOG-E1105, which randomly assigns women to paclitaxel with trastuzumab and optional carboplatin and then randomly assigns them bevacizumab or not.

I have a patient on ECOG-E1105 who is exactly like this woman, and if she has a complete response to chemotherapy, we will proceed with local therapy for her primary tumor — whether that is lumpectomy or radiation therapy or axillary dissection — continue trastuzumab and then add in hormone therapy.

If she has a complete response to her initial therapy, hormone therapy will offer

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel/carboplatin</td>
<td>53%</td>
</tr>
<tr>
<td>Nab paclitaxel</td>
<td>15%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>14%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>12%</td>
</tr>
<tr>
<td>TC</td>
<td>3%</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Note: n = 59 who would recommend trastuzumab*

If she is totally asymptomatic, has a single liver metastasis and has no evidence of end-organ dysfunction, we have lots of wiggle room. I would probably start her with endocrine therapy, with the specific choice dependent on what we wish to accomplish.

It would be reasonable to start her on tamoxifen. One could also make a case for tamoxifen and trastuzumab, but then she is tethered to your clinic because she will have to come in every three weeks for IV administration. Others would use ovarian ablation and tamoxifen. Data suggest that the response rate is higher with the combination, but no data indicate that survival is improved with that approach.

One could administer chemotherapy/trastuzumab, but what is the objective of that approach? This woman is in no danger of dying from her disease in the next two months. In fact, she’s in no danger of having substantial end-organ dysfunction that would preclude her from receiving chemotherapy and bevacizumab down the road.

Evidence does not indicate that she will live longer by receiving up-front chemotherapy/trastuzumab. You will be subjecting her to toxicities that she can probably avoid — although, frankly, you will be administering this treatment down the road.

If the treating oncologist consulted with me and expressed a desire to treat her with chemotherapy/trastuzumab, I wouldn’t argue strongly against that approach — it’s simply not what I would do.

**FIGURE 15**

**For this patient, if you would recommend trastuzumab or lapatinib with or without endocrine therapy, which chemotherapy agent(s) would you most likely combine with your anti-HER2 agent?**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel/carboplatin</td>
<td>53%</td>
</tr>
<tr>
<td>Nab paclitaxel</td>
<td>15%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>14%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>12%</td>
</tr>
<tr>
<td>TC</td>
<td>3%</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Note: n = 59 who would recommend trastuzumab*

<table>
<thead>
<tr>
<th>Decision</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>39%</td>
</tr>
<tr>
<td>No</td>
<td>37%</td>
</tr>
<tr>
<td>No, but I would consider radiofrequency ablation (RFA)</td>
<td>24%</td>
</tr>
</tbody>
</table>

*Note: n = 59 who would recommend trastuzumab*
her the best chance of long-term survival. With that goal in mind, I would make certain that her ovaries were fully suppressed or removed and then I would administer tamoxifen to maximize the benefit of her hormone therapy. The difficult question is how long to continue trastuzumab if she has a complete response. Treatment until progression reverts to the mind-set that the disease is not curable. I have an equal number of women who pick an arbitrary time to discontinue trastuzumab and others who continue trastuzumab.

If she doesn’t have a complete response, then the best data we have indicate she does not have the possibility of long-term survival and we need to shift our goals to preserving the quality of her life while still trying to extend it. So we would perhaps make different decisions about local therapy, about more aggressive hormone therapy and about how long we might continue the trastuzumab.

**DR HAYES:** I don’t believe that resecting a liver metastasis does any good in breast cancer. The data simply do not support that approach.

Many years ago, Don Morton performed metastatectomies on a variety of sites and suggested that those patients who had a metastatectomy lived longer than those who did not, but of course he chose patients who were most likely to be able to undergo the resection.

If you can perform the resection of the liver metastasis laparoscopically and do it safely, then it may be okay. However, any time you touch a patient with a procedure, a risk is incurred, and I don’t see any evidence that this will improve her outcome.

I have sent patients for isolated hepatic treatment, but more commonly at our institution it’s a radiation therapy approach. Our group is not performing RFA, but I believe it’s reasonable.

Frankly, most of us would only do this for patients who have an isolated liver metastasis and a long disease-free interval, which are the patients who will live a long time anyway. I might consider local treatment for the hepatic lesion if the patient wanted to avoid systemic therapy for the next couple of years, but I don’t believe you will cure the patient.

**DR MILLER:** I can’t say that resection of the liver metastasis is an unreasonable consideration for a patient who, by your best imaging, has one lesion, but I’m not a fan of this approach and, in general, I haven’t done that. The bulk of the data that we have suggests that one lesion is the one you can see but many more exist that you cannot see.

RFA is another approach that’s often brought up as a way of administering local therapy but perhaps with less toxicity and less recovery time than surgery. However, I don’t believe it will meaningfully change her likelihood of being a long-term survivor or the quality of her life. So it’s not something that I’ve recommended to patients in this situation.
COMMENT FROM THE TREATING PHYSICIAN

KENNETH R HOFFMAN, MD, MPH:
The patient accepted anastrozole and trastuzumab and had a dramatic response. The tumor in the breast is now resectable and the lung masses have essentially disappeared.

The question now is whether to perform a proactive mastectomy for local tumor control, which she's willing to do, or do we simply continue systemic therapy indefinitely?

Select Commentary from Interviews Conducted at SABCS 2008

DR HAYES: All of us have patients like this, and I find them both challenging and rewarding. As in society in general, if all of our patients thought exactly alike it would be a boring place.

These patients enrich our practice, and I enjoy taking care of them. It’s always sad when a patient refuses therapy — out of...I don’t want to say ignorance because that sounds pejorative, but out of a lack of understanding of what we can do for them with few side effects.

The challenge is to help this patient understand that we can do her a lot of good without a lot of toxicity. This is when a thoughtful and compassionate physician and, more importantly, nurse, can be of great value. My nurse practitioner routinely saves me because she loves these folks and gets involved.

I would recommend anastrogen therapy for this patient and would probably add trastuzumab. My guess is that she’ll fare reasonably well with that.

I would probably recommend removal of the breast lesion for palliation, depending on how much response she’s had to systemic therapy. Then the question is whether to resect the lesion and add...
radiation therapy or simply irradiate the lesion if she’s had a nice response. These treatments will not prolong her survival, but the goal is to keep the lesion from breaking down in the future.

In my practice, we probably see six to 10 cases like this each year. Granted, we serve several million people, and we find it’s not only the uneducated person who delays seeking medical attention. Indeed, the patient may be well educated. My impression is that it’s a mixture of people from all walks of life.

I believe, although I’ve never seen this documented, that these cases involve a fair amount of spirituality. Some people believe their faith will lead them through, so they keep ignoring the issue. It behooves us to work with that theory, so I try to make patients understand that I want to work with them involved with a psychologist.

For now, whether to remove the primary tumor is patient dependent, but the cases in which I consider it involve low-volume metastatic disease, typically when a response to therapy has occurred and, in particular, when a patient, upon hearing that it’s not clear what to do, feels strongly about wanting to do something in the way of local therapy.

**DR BURRIS:** I’ve seen two patients like this in the past six months, and both had extenuating life circumstances that contributed to their delay in seeking treatment.

One lost her home in a tornado, and the other had a spouse who was ill. So some women neglect to come in not because they don’t want medical care but because they put their family first and end up with a late diagnosis.

We have to assess the situation and find out what all the factors are that caused them to delay seeking care. If it really is a situation of significant denial associated with depression, then we get them involved with a psychologist.

For some patients, their initial inclination is that they don’t want chemotherapy, but that may change after they speak with you. It’s a day-to-day decision, and we must be open minded about how we treat these patients.

Although this woman says she won’t take chemotherapy, she still has many choices, and it’s quite a decision. She could take any one of three aromatase inhibitors or tamoxifen or fulvestrant. She also could choose biologics — lapatinib, trastuzumab or bevacizumab — and they can also be combined.

We have data on all these agents. In addition, she could at some point consider entering a clinical trial of trastuzumab-DM1.

**DR GRALOW:** We sometimes see patients who refuse any kind of therapy from a conventional provider, but we do the best we can for these patients and we try to be there if they change their mind.

I’ve had patients whom I referred, at their request, to a naturopath, and I’ve continued to follow them jointly.

Eventually most of these patients come back to us for some form of systemic therapy, sometimes when they become symptomatic or frightened enough that they want to be more aggressive.

I’m certain a few have never come back for treatment, but regardless, I believe our job is to be there for them, listen to their concerns and work with them.
I would biopsy the lesion, depending on what the patient wanted to do. The alternative is probably one of the best therapies we have, and that’s tamoxifen. By switching her from an aromatase inhibitor to tamoxifen, we are administering a different antiestrogen therapy, and even if it doesn’t benefit her, I don’t believe it will cause any harm.

WILLIAM J GRADISHAR, MD: I wouldn’t have ordered imaging studies for this patient. However, once I knew the disease was present, I would start endocrine therapy in addition to a bisphosphonate. I believe that exemestane and fulvestrant are equivalent choices, and a case could even be made for tamoxifen.

Biopsies of bone-only metastases can be problematic because a negative result can be caused by a sampling error. So one can make a case for treating empirically with endocrine therapy. However, if the patient developed any visceral or soft tissue disease that could be biopsied easily, I would do so.

In cases such as this one, treatment is palliative, not curative, so the goals of selecting an endocrine therapy include delaying the time until chemotherapy is needed and maintaining quality of life. In managing metastatic disease, we don’t have to see the lesions disappear. Stable disease is an acceptable endpoint, and it has an outcome that’s equivalent to objective response. This concept is now used with chemotherapy, but it was initially identified with endocrine therapy.

Certainly with bone-only disease, evidence supports continuing endocrine therapy.

Also, this is a case in which I believe circulating markers can be helpful. If the patient has circulating tumor cells or an elevated CA15-3 in the 50 to 100 units/L range, that indicates metastatic breast cancer, and it could be almost nothing else.

If the bone metastasis consisted of an isolated, single focus and the plain films and markers were negative, I would either do nothing and repeat the scan later, or...
therapy as long as you don’t see disease progression. It would be great if all evidence of metastases disappeared, but if the bone scan remains stable, that’s acceptable. I would use endocrine therapy to the point of exhaustion, as long as the patient doesn’t develop a visceral crisis or another problem that motivates us to use chemotherapy. A fraction of patients will respond to successive maneuvers with different endocrine agents.

We’ve spent 20 years trying to figure out which endocrine agent or sequence is best in these cases. The bottom line is that it probably doesn’t make a big difference. You can switch between classes of endocrine therapy, or within the class of aromatase inhibitors you can switch between a steroidal and a nonsteroidal aromatase inhibitor. In EFECT, fulvestrant was compared to exemestane among patients whose disease progressed on a nonsteroidal aromatase inhibitor, and the outcomes were absolutely identical regarding side effects, clinical benefit rate, objective response rate and time to disease progression.

One of the questions this case brings up is whether we should order general screening tests for asymptomatic patients such as this one. I believe that the simple answer is no. This is a difficult issue to explain to patients. To illustrate that point, only a few days ago, a group of clinicians, including myself, Cliff Hudis and Hal Burstein, were meeting with a group of patient advocates. We were to update what was new in the NCCN guidelines.

The first point was whether we should conduct PET scanning, tumor markers, etc., for these patients. Cliff succinctly answered, “Absolutely not.” After 45 minutes, we were still trying to explain to the advocates why it isn’t a good thing for a patient who is otherwise well. The fact is that we have little evidence that identifying asymptomatic metastatic disease sooner, whether it’s two weeks or two months, will make a significant difference in overall outcomes for patients, but this can be a difficult concept for some patients to understand.
Select Commentary from Interviews Conducted at SABCS 2008

DR HAYES: This patient’s disease may or may not be endocrine refractory. She’s never received tamoxifen, which is a good drug. However, she is developing end-organ dysfunction, and this patient doesn’t have a lot of wiggle room. She already has shortness of breath.

If you administer tamoxifen and two or three months later you discover that was the wrong choice, then you’re in trouble. Her symptoms will be much worse, which makes it even more difficult to administer chemotherapy.

So I would probably proceed with chemotherapy and use paclitaxel/bevacizumab, which seems like the perfect first-line therapy.

Because this patient had a great response to nab paclitaxel, Dr Hart questioned whether he should administer bevacizumab or whether he could administer it with another, second-line chemotherapy when the disease progresses.

I don’t believe we’re obligated to use bevacizumab with a taxane up front. I would probably administer bevacizumab as first-line therapy because we have a prospective, randomized trial suggesting that time to disease progression is prolonged.

If you are in a practice in which bevacizumab is not a viable option, I can’t argue that it’s the wrong decision. Let’s recall that the taxanes are effective and our goal is palliation, so a taxane by itself is appropriate.

In terms of administering bevacizumab after she progresses on the taxane, we are getting outside of evidence-based data. We don’t have evidence that the next line of therapy with or without bevacizumab is better. We know that after progression on a couple of prior therapies, capcitabine in combination...
With bevacizumab is not effective. I have used bevacizumab in that setting, and a couple of patients have fared well.

Was that because of the bevacizumab or because the next chemotherapy was effective? I don’t know, so I don’t believe there’s a right or wrong answer.

I have spoken at great length with Kathy Miller, who is probably the leading investigator of bevacizumab in breast cancer, and she doesn’t believe the benefits in the ECOG-E2100 trial of paclitaxel/bevacizumab are specific to bevacizumab.

She believes that the specific chemotherapeutic agent doesn’t matter. Rather, it’s the earlier use that likely makes it more effective. Biology is consistent with that belief. Once angiogenesis is turned on, it is difficult to get rid of it compared to preventing new angiogenesis and, therefore, new metastases.

When I have a patient with metastatic disease for whom I’m considering first-line therapy, I ask the patient, “Do you want to take a pill or do you want IV therapy?”

This woman has bone metastases, so you will use bisphosphonates anyway, and it probably won’t matter to her if she receives IV chemotherapy. If she had lung-only metastases and you didn’t want to administer bisphosphonates, it would be reasonable to administer capecitabine by itself.

If nab paclitaxel had been developed as the first taxane and was off patent now and inexpensive, it would be our drug of choice. Unfortunately, nab paclitaxel was our third taxane, and the benefits compared to standard paclitaxel are not great.

The occasional patient who has terrible reactions to standard paclitaxel probably doesn’t experience the same reactions with nab paclitaxel. You may also be able to administer nab paclitaxel a little longer because it’s more likely to be effective.

DR GRALOW: I probably would have opted for paclitaxel and bevacizumab. Also, it would be reasonable to enroll this patient on the CALGB-40502 trial, evaluating paclitaxel/bevacizumab versus nab paclitaxel/bevacizumab versus ixabepilone/bevacizumab.

I’m impressed with nab paclitaxel and find it easier to administer than paclitaxel. It doesn’t require premedications, we see less allergic reactions and patients prefer it. In many cases we seek insurance preauthorization and, if we obtain it, then that’s my choice. If not, I choose paclitaxel.

DR BURRIS: If a patient has triple-negative breast cancer, then I typically decide to use weekly paclitaxel and bevacizumab. I am certainly influenced by the ER/PR positivity, and if a patient is asymptomatic, then I may start out with weekly paclitaxel or capecitabine. However, the data are much weaker for bevacizumab in the second- or third-line setting, so I find fewer and fewer patients for whom I don’t offer a taxane with bevacizumab up front.
COMMENT FROM THE TREATING PHYSICIAN

MICHAEL A SCHWARTZ, MD:
This is the only patient I have treated with bevacizumab who had symptomatic nephrotic syndrome. This patient responded to bevacizumab treatment and then progressed off of it. The nephrotic syndrome was reversible. She experienced proteinuria but did not have a significant increase in her creatinine. So is it worth the risk of rechallenging with bevacizumab in this type of situation?

Select Commentary from Interviews Conducted at SABCS 2008

DR HAYES: The development of nephrotic syndrome with bevacizumab has been reported, but it is uncommon. I agree with George Sledge and Kathy Miller, who commented that, in general, bevacizumab is a well-tolerated drug with occasional serious adverse effects. These include hemorrhage, hypertension and renal dysfunction. In this patient, I would not have pushed the bevacizumab. I probably would have used it as this physician did, but at the first sign of nephrotic syndrome, I would have stopped it because I don’t believe you will improve her survival much with it, and you’re making her sicker rather than better.

DR MILLER: I have seen nephrotic-range proteinuria, but without the other symptoms of nephrotic syndrome, in two patients. Grade III/IV proteinuria occurs in only about three percent of patients treated with bevacizumab.

I would stop the bevacizumab for this patient. She has developed two major bevacizumab-associated toxicities. She had difficult-to-control hypertension, which is also a rare situation. She received a modest reexposure to bevacizumab with capecitabine and had more trouble with hypertension and nephrotic-range proteinuria. Her disease is progressing, and we don’t have any data that continuing bevacizumab beyond disease progression is helpful.

Which chemotherapy, if any, would you recommend for this patient?

Would you restart the bevacizumab with the chemotherapy?

If not, would you consider retreatment with bevacizumab at some later time for this patient?
SELECT PUBLICATIONS

CASE 6

CASE 7

CASE 8
Chia S et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: Results from EFECT. J Clin Oncol 2006;24(10):1664-70. [Abstract]

CASE 9


Johnston S et al. Lapatinib combined with letrozole vs letrozole alone for front line postmenopausal hormone receptor positive (HR+) metastatic breast cancer (MBC): First results from the EGF30008 Trial. SABCS 2008; Abstract 46.


Perspectives on Systemic Treatment of Early Breast Cancer
Highlights from a survey performed in conjunction with a satellite education symposium at the American Society of Breast Surgeons annual meeting, New York, May 1, 2008

J MICHAEL DIXON, MD: Semiglazov and colleagues randomly assigned patients with ER-positive breast cancer to neoadjuvant chemotherapy versus an aromatase inhibitor and reported similar response rates, with more women achieving breast-conserving surgery with endocrine therapy. The reason is that pathologic changes within a tumor are different with endocrine therapy versus chemotherapy. From our studies we learned that the longer you treat, the better response you obtain. We’ve been treating patients for longer durations with endocrine therapy — nine months to one year instead of three to four months. You can eventually convert approximately 70 percent of these patients — with strongly ER-positive, usually PR-positive disease — from requiring a mastectomy for locally advanced breast cancer to candidates for breast-conserving surgery.

FIGURE 27
You are evaluating a patient with small breasts who underwent a biopsy of a 3-cm, ER++, HER2-negative IDC in the inferior pole of the right breast and would have an unacceptable cosmetic outcome with standard partial mastectomy. The patient wishes to have breast-conserving surgery. Which treatment would you most likely recommend for the following patients?

40-year-old, premenopausal patient

70-year-old patient

55-year-old, postmenopausal patient

PO = practicing oncologists; CIS = clinical investigator surgeons; GS = general surgeons
During the past two years, the issue of smaller, ER-positive, HER2-negative, node-negative tumors has become an area of contention and enormous expectation. Ordinarily, patients with ER-positive disease would most likely receive endocrine therapy, but the question is, would they benefit from chemotherapy in addition to hormone therapy?

The idea is that we’ll be able to identify patients who will obtain a particularly low degree of benefit from chemotherapy and be able to prevent overtreatment. The hope is that we will revolutionize treatment for patients with ER-positive disease who are at low risk.

One line of thought is that molecular markers will allow us to use the multi-gene assays as in the NSABP-B-20 study, which demonstrated that patients with low Oncotype DX Recurrence Scores® did not benefit from chemotherapy.

At the 2007 San Antonio Breast Cancer Symposium, SWOG presented the S8814 trial data evaluating the Oncotype DX assay for patients with positive nodes who received tamoxifen and were then randomly assigned to chemotherapy or not. Again, the low-risk molecular signature identified patients who did not seem to benefit from the addition of chemotherapy to endocrine therapy.

For a patient whose tumor is 1+ on IHC, I order FISH. What does 1+ mean? In the ASCO/CAP guidelines, it is assumed that HER2 testing is performed by a validated IHC assay. If the assay has not been validated, then we don’t know what 1+ means. If
a laboratory used a validated IHC assay, then I would have more confidence in the result, but in my own practice I would still order FISH. Guidelines are established to define a minimum standard to which everyone should conform. It doesn’t mean that we cannot do better than what the guidelines recommend.

**DR DIXON:** MA17 was a seminal study that reeducated us that among patients with hormone receptor-positive breast cancer, more events occur from years five to 15 than in the first five years. I believe that everyone is more aware now that the risk of recurrence is almost lifelong. The rate of contralateral or second breast primaries in treated patients continues at the same rate almost forever.

**DR RAVDIN:** We have all seen disappointing circumstances in which disease recurs after 10 years. The data indicate that recurrence risk is stable during the first five years, with a substantial risk in years five to 10.
Between years five and 10, patients with node-positive disease have approximately a 20 percent risk of recurrence. Patients with node-negative disease have a 10 percent risk. This is true for patients with hormone receptor-positive tumors, but it’s not true for those with hormone receptor-negative tumors, who experience most of their recurrences within the first five years.

Currently, one of the major unanswered questions is whether to continue therapy after a patient completes five years of an adjuvant aromatase inhibitor. In the Intergroup study MA17, a marked benefit was observed with letrozole for patients who had completed five years of adjuvant tamoxifen.

These patients had hormone receptor-positive tumors, so their risk of recurrence was substantial and it was reduced by the extended use of an aromatase inhibitor.

**SELECT PUBLICATIONS**


PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

<table>
<thead>
<tr>
<th></th>
<th>4 = Excellent</th>
<th>3 = Good</th>
<th>2 = Adequate</th>
<th>1 = Suboptimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Continuation of an aromatase inhibitor beyond five years in a postmenopausal patient with ER-positive breast cancer</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Optimizing trastuzumab for patients with HER2-positive breast cancer in the adjuvant setting</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Oncotype DX assay in node-negative and node-positive early breast cancer</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Adjuvant treatment strategies for patients with triple-negative breast cancer</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Options for sequencing and combining anti-HER2 agents for patients with HER2-positive disease progressing on trastuzumab</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sequence of endocrine therapies for pre- and postmenopausal patients with ER-positive, metastatic disease</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Risk-benefit profiles of available taxanes and antitubulin agents with or without bevacizumab</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

<table>
<thead>
<tr>
<th></th>
<th>4 = Excellent</th>
<th>3 = Good</th>
<th>2 = Adequate</th>
<th>1 = Suboptimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Continuation of an aromatase inhibitor beyond five years in a postmenopausal patient with ER-positive breast cancer</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Optimizing trastuzumab for patients with HER2-positive breast cancer in the adjuvant setting</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Oncotype DX assay in node-negative and node-positive early breast cancer</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Adjuvant treatment strategies for patients with triple-negative breast cancer</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Options for sequencing and combining anti-HER2 agents for patients with HER2-positive disease progressing on trastuzumab</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sequence of endocrine therapies for pre- and postmenopausal patients with ER-positive, metastatic disease</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Risk-benefit profiles of available taxanes and antitubulin agents with or without bevacizumab</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Was the activity evidence based, fair, balanced and free from commercial bias?
☐ Yes  ☐ No

Please explain: ____________________________________________________________

Will this activity help you improve patient care?
☐ Yes  ☐ No  ☐ Not applicable

If no, please explain: ______________________________________________________

Did the activity meet your educational needs and expectations?
☐ Yes  ☐ No

If no, please explain: _____________________________________________________

Please respond to the following LEARNER statements by circling the appropriate selection:

<table>
<thead>
<tr>
<th>4 = Yes</th>
<th>3 = Will consider</th>
<th>2 = No</th>
<th>1 = Already doing</th>
<th>N/M = Learning objective not met</th>
<th>N/A = Not applicable</th>
</tr>
</thead>
</table>

AS A RESULT OF THIS ACTIVITY, I WILL BE ABLE TO:

• Compare treatment strategies utilized by community oncologists, general surgeons and cancer clinical investigators in the primary, adjuvant and metastatic settings, and apply this information to the routine management of breast cancer.

• Evaluate clinical issues for which relative agreement and heterogeneity exist in patterns of breast cancer care, and make treatment decisions considering this information.

• Counsel patients with breast cancer about the benefits and risks of multiple acceptable treatment options when they exist.

• Recognize the rate at which practice-changing clinical research impacts physician decision-making, and explain how this affects oncology patient access to standard and novel therapies.

• Recall the design and eligibility criteria for ongoing breast cancer clinical trials, and consider appropriate patients for study participation.

What other practice changes will you make or consider making as a result of this activity?

__________________________________________________________

What additional information or training do you need on the activity topics or other oncology-related topics?

__________________________________________________________
Additional comments about this activity:

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity 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 am willing to participate in a follow-up survey.  ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty for this educational activity

To what extent do you feel the faculty members’ comments were helpful or not helpful?

Please be as specific as possible about individual faculty.

Please recommend additional faculty for future activities:

Other comments about the faculty for this activity:

REQUEST FOR CREDIT — Please print clearly

Name: ................................................................. Specialty: ..........................................................

Professional Designation:

☐ MD ☐ PharmD ☐ NP

☐ DO ☐ RN ☐ PA ☐ Other ...........................................

Medical License/ME Number: .................. Last 4 Digits of SSN (required): ..................

Street Address: ................................................. Box/Suite: ..........................................

City, State, Zip: ..................................................

Telephone: ..................................................... Fax: ..........................................

Email: ..............................................................

Research To Practice designates this educational activity for a maximum of 2.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be ______________ hour(s).

Signature: .......................................................... Date: .............................................

To obtain a certificate of completion and receive credit for this activity, please fill out the Educational Assessment and Credit Form and fax to (800) 447-4310, or mail to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Educational Assessment online at www.ResearchToPractice.com/POC/Breast.
Management of Breast Cancer in the Adjuvant and Metastatic Settings

750 Second Opinions: Survey of Oncologists in Practice Regarding 10 Cases Presented by Their Colleagues

Interdisciplinary Perspective: Survey Comparing Responses of Surgical and Medical Oncology Investigators and Surgeons and Medical Oncologists in Practice

Editor
Neil Love, MD