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Breast Cancer® UPDATE

An Audio Review Journal for Surgeons

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

INTERVIEWS

Pat W Whitworth Jr, MD

Dennis J Slamon, MD, PhD

Paul E Goss, MD, PhD

Thomas B Julian, MD

Daniel F Hayes, MD

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Breast Cancer Update for Surgeons
A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic techniques, 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 breast surgeon must be well informed of these advances. To bridge the gap between research and patient care, *Breast Cancer Update* for Surgeons utilizes one-on-one discussions with leading breast cancer investigators. By providing access to the latest research developments and expert perspectives, this CME program assists breast surgeons in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer in order to incorporate these data into management strategies in adjuvant and neoadjuvant disease.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of aromatase inhibitors in the adjuvant and neoadjuvant settings and of switching to or sequencing aromatase inhibitors after tamoxifen.
- Develop an algorithm for ER and HER2 testing and implement a treatment plan for patients with HER2-positive breast cancer.
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer.
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions.
- Counsel appropriately selected patients about availability and applicability of emerging research data on sentinel lymph node biopsy.
- Discuss the risks and benefits of partial breast irradiation and the clinical trials evaluating this technique with appropriately selected patients.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE* FOR SURGEONS

The purpose of Issue 3 of *Breast Cancer Update* for Surgeons is to support these global objectives by offering the perspectives of Drs Whitworth, Slamon, Goss, Julian and Hayes on the integration of emerging clinical research data into the management of breast cancer.

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IN THIS ISSUE OF *BREAST CANCER UPDATE* FOR SURGEONS

- Sentinel lymph node biopsy in the neoadjuvant setting
- Management of patients with ductal carcinoma in situ (DCIS)
- Role of the Onco*type* DX™ assay in clinical decision-making regarding adjuvant systemic therapy
- TAILORx (Trial Assigning IndividuaLized Options for Treatment [Rx])
- Long natural history of hormone receptor-positive breast cancer and implications for extended adjuvant endocrine therapy
- American College of Surgeons Oncology Group neoadjuvant trial Z1031 evaluating anastrozole versus letrozole versus exemestane
- NSABP-B-39: Partial breast irradiation (PBI) versus whole breast radiation therapy
- Quality assurance and testing algorithm for HER2 and ER/PR
- Overview of the efficacy and safety of adjuvant trastuzumab in HER2-positive early breast cancer

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INTERVIEW

Pat W Whitworth Jr, MD

Dr Whitworth is Director of the Nashville Breast Center and Clinical Associate Professor of Surgery at Vanderbilt University in Nashville, Tennessee.

Tracks 1-14

Select Excerpts from the Interview

Tracks 5-6

DR LOVE: Would you discuss the NSABP-B-39 (1.1) trial and where we are right now in terms of partial breast irradiation?

DR WHITWORTH: The most interesting aspect of B-39 is that it is answering the questions that those of us who are using partial breast irradiation are asking: Can it be used for patients with positive nodes? Can it be used for patients at high risk — younger patients or patients with lobular tumors?

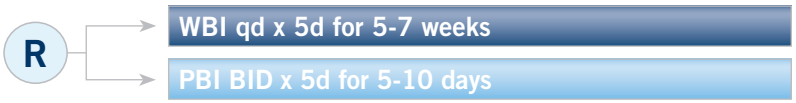
DR LOVE: What's your preferred method of PBI?

DR WHITWORTH: It depends on the patient. Some patients require the multi-

1.1

A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) versus Partial Breast Irradiation (PBI) for Women with Stage 0, I or II Breast Cancer

Protocol IDs: NSABP-B-39/RTOG 0413
Target Accrual: 4,300 (Open)



Eligibility

- Stage 0, I or II breast cancer resected by lumpectomy
- Tumor size ≤ 3 centimeters
- No more than three histologically positive nodes

Primary Endpoint

- Time to in-breast tumor recurrence

In both arms, adjuvant chemotherapy (two weeks prior to WBI or two weeks post-PBI)

In patients with ER-positive or PR-positive disease, hormonal therapy three to 12 weeks after adjuvant chemotherapy (before, during or after WBI/PBI for patients not receiving adjuvant chemotherapy for five years)

SOURCE: NCI Physician Data Query, November 2007.

catheter approach, whereas others are better off with a balloon and still others fare better with 3D conformal.

I prefer the balloon approach because it irradiates less breast tissue than the 3D conformal. Studies evaluating how much tissue volume actually receives the target dose demonstrate superiority for the balloon approach, mainly because the apparatus is held in a fixed place.

Breathing has no effect, so the target dose is delivered more uniformly even than in some of the multicatheter analyses (Weed 2005).

DR LOVE: If PBI turns out to be an acceptable approach, how much of an advantage will it offer women?

DR WHITWORTH: It's a big advantage. We were shocked to find that approximately 15 percent of women do not receive radiation therapy because they live too far from the facility (Athas 2000). The farther they live away from the facility, the more likely they are to not receive it.

Thus the five-day cycle with the balloon is helpful to a lot of women. The other aspect that makes it more practical for women who live far away from the facility is that the American Cancer Society has arranged a place where people can stay for a few days while receiving treatment.

Tracks 10-11

DR LOVE: How do you see the Onco*type* DX assay fitting into clinical practice now and evolving for the future?

DR WHITWORTH: This assay is one of the most exciting developments in breast cancer in a long time. Surgeons and oncologists now have a way of deciding which patients will benefit from systemic adjuvant chemotherapy. Historically, we've all been frustrated because in some situations, out of 100 women, perhaps six will have their lives saved by adjuvant chemotherapy. As a result, we have treated a number of women who didn't need it — we just couldn't determine who did and who didn't. This genomic assay is now allowing us to identify those groups of women.

DR LOVE: The assay also has the potential to identify patients to whom oncologists possibly wouldn't have administered chemotherapy based solely on small tumor size.

DR WHITWORTH: Exactly. In fact, identifying this kind of patient keeps us going. It's like putting on glasses that allow you to see something you couldn't see before. You see not only the patients who don't need it but also the patients who by conventional criteria wouldn't be treated and you'd miss.

Track 12

DR LOVE: Could you review the ACOSOG study (1.2) on neoadjuvant aromatase inhibitors?

DR WHITWORTH: It's critical for surgeons to be involved in neoadjuvant trials in which you can obtain a biopsy of the lesion prior to some intervention — whether it's an aromatase inhibitor or something else — and then excise the tumor and see what the biological effects have been. It's also of practical importance because now we're identifying patients in whom we believe hormonal neoadjuvant therapy will be much more appropriate than neoadjuvant chemotherapy. Generally, those are postmenopausal women with ER-positive disease.

If you look at the information from the 21-gene (Onco*type* DX) assay studies, patients who have a low likelihood of a great response to neoadjuvant chemotherapy seem to be the patients who have a better likelihood of benefit from hormonal therapy. So we are expecting to improve the breast conservation rate with neoadjuvant hormonal therapy in that series. That series will set up a much larger study to compare neoadjuvant hormonal therapy to neoadjuvant chemotherapy in the future.

DR LOVE: Have you enrolled patients on this study?

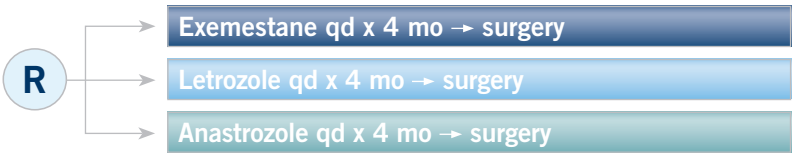
DR WHITWORTH: Yes, and we have seen good responses. Furthermore, the patients who have received neoadjuvant hormonal therapy have been happy

with it. It's statistically unlikely that metastasis could happen in this short time, and most patients respond. We do expect to see confirmation of higher rates of breast conservation. ■

1.2

Phase III Randomized Study of Neoadjuvant Therapy Comprising Exemestane versus Letrozole versus Anastrozole in Postmenopausal Women with Estrogen Receptor-Positive Stage II or III Breast Cancer

Protocol ID: ACOSOG-Z1031
Accrual: 375 (Open)



Eligibility

- Postmenopausal
- ER-positive tumor with an Allred score of 6, 7 or 8

Study Contacts

American College of Surgeons Oncology Group
Matthew Ellis, MD, PhD, FRCP, Protocol Chair
Tel: 314-362-8866
John Olson, MD, PhD, Protocol Co-Chair
Tel: 919-684-6523

Cancer and Leukemia Group B
Kevin Hughes, MD, FACS
Principal Investigator
Tel: 617-724-4800

SOURCE: NCI Physician Data Query, November 2007.

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Ellis M et al. **Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial.** *J Clin Oncol* 2001;19(18):3795-7. **Abstract**

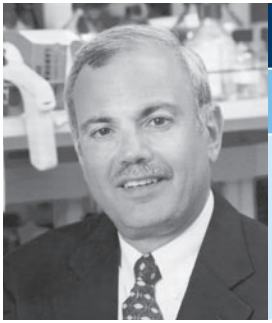
Ellis M. **Preoperative endocrine therapy for older women with breast cancer: Renewed interest in an old idea.** *Cancer Control* 2000;7(6):557-62. **Abstract**

Murray J et al. **Letrozole and anastrozole: A pre-operative study of their effects on ER positive breast cancers in postmenopausal women.** Poster. San Antonio Breast Cancer Symposium 2004;**Abstract 406**.

Semiglazov V et al. **The relative efficacy of neoadjuvant endocrine therapy vs chemotherapy in postmenopausal women with ER-positive breast cancer.** ASCO 2004;**Abstract 519**.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) and Genomic Health, Inc announce positive study results demonstrating Onco*type* DX genomic breast cancer assay predicts chemotherapy response. Press Release.

Weed DW et al. **Accelerated partial breast irradiation: A dosimetric comparison of three different techniques.** *Brachytherapy* 2005;4(2):121-9. **Abstract**



INTERVIEW

Dennis J Slamon, MD, PhD

Dr Slamon is Professor of Medicine, Chief of the Division of Hematology/Oncology and Director of Clinical/Translational Research at the David Geffen School of Medicine at UCLA's Jonsson Comprehensive Cancer Center in Los Angeles, California.

Tracks 1-5

Track 1 Clinical trials of adjuvant trastuzumab

Track 2 Efficacy and cardiotoxicity of adjuvant trastuzumab in a nonanthracycline-based regimen

Track 3 Trastuzumab monotherapy

Track 4 Efficacy of trastuzumab in patients with small, node-negative, HER2-positive tumors

Track 5 Assessment of HER2 status by FISH versus IHC

Select Excerpts from the Interview

Track 1

DR LOVE: Can you review the results from the adjuvant trastuzumab trials?

DR SLAMON: Within about a year, four adjuvant trastuzumab trials reported essentially the same benefit. The benefit was larger than anticipated, and all of the trials were massively overpowered. Among the four trials, there were 13,000 patients randomly assigned to a trastuzumab- versus a nontrastuzumab-based therapy.

The trials demonstrated approximately a 50 percent reduction in the risk of recurrence and a 30 percent improvement in survival for patients who received trastuzumab (Joensuu 2006; Piccart-Gebhart 2005; Romond 2005; Slamon 2006; [2.1]).

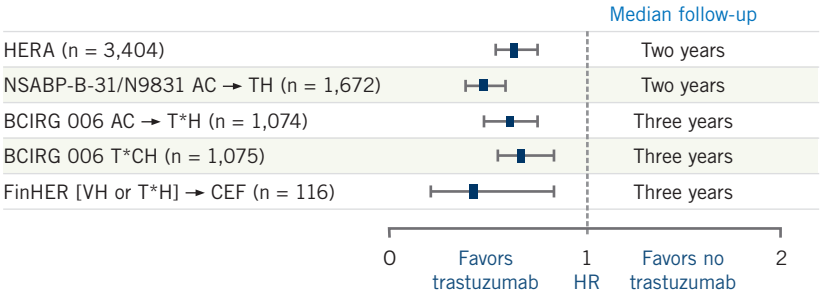
DR LOVE: What about side effects and toxicities associated with adjuvant trastuzumab?

DR SLAMON: The only important toxicity associated with trastuzumab has been cardiotoxicity, in particular when used in combination with anthracycline-based chemotherapy.

Otherwise, trastuzumab is a forgiving drug. It does not have any of the side effects associated with our usual chemotherapies or even some of our hormonal therapies.

2.1

Hazard Ratios (HR) for Disease-Free Survival in Adjuvant Trastuzumab Trials (n = 7,341)



H = trastuzumab; T = paclitaxel
T* = docetaxel; V = vinorelbine

SOURCES: Smith I et al. *Lancet* 2007;369(9555):29-36. **Abstract**; Slamon D et al. *Proc SABCS* 2006;**Abstract 52**; Joensuu H et al. *N Engl J Med* 2006;354(8):809-20. **Abstract**; Romond EH et al. *N Engl J Med* 2005;353(16):1673-84. **Abstract**

Track 2

DR LOVE: The BCIRG 006 trial, which you led, was the only study evaluating trastuzumab with a nonanthracycline-containing regimen — TCH (docetaxel/carboplatin/trastuzumab). What did you see?

DR SLAMON: We saw no increase in cardiotoxicity over AC → T (doxorubicin/cyclophosphamide → docetaxel; [Slamon 2006]). In terms of efficacy, the updated analysis of BCIRG 006 demonstrated that both experimental arms, AC → TH (doxorubicin/cyclophosphamide → docetaxel/trastuzumab) and TCH, were superior to the nontrastuzumab-containing regimen (Slamon 2006).

No data demonstrate that an anthracycline adds incremental benefit compared to a nonanthracycline regimen with trastuzumab. If you use the nonanthracycline regimen, TCH, you see exactly the same benefit as the anthracycline-based regimen — the curves are identical. They overlap completely.

So most patients derive no benefit from anthracycline-based therapy with trastuzumab in terms of an incremental improvement, but they derive all the toxicity, cardiomyopathies, congestive heart failure, leukemia and myelodysplasia. Therefore, I don't believe there's a role for anthracyclines in the adjuvant setting when you are using trastuzumab.

Tracks 3-4

DR LOVE: What about using adjuvant trastuzumab without chemotherapy in the older or the frail patient?

DR SLAMON: Off study, we've done that at our institution a number of times — any time we think there may be a complication from chemotherapy.

However, data show that irrespective of chronologic age, if the patient has a good performance status, she benefits from chemotherapy. So we want to offer the elderly patients every advantage.

That said, we shouldn't look for trouble. We know that certain regimens could cause problems when used together. If any kind of dysfunction or performance status issues exist, I think trastuzumab monotherapy makes sense. However, we have no clinical trial data to support that.

DR LOVE: What about patients with node-negative, HER2-positive disease — particularly smaller tumors?

DR SLAMON: The data, thus far, have demonstrated that the relative benefit for a patient with node-negative disease appears to be similar to the benefit for a patient with node-positive disease in terms of the relative risk reduction (Slamon 2006).

In terms of tumor size — greater than two centimeters or less than two centimeters — it looks as if the benefit may be the same in both of those groups (Slamon 2006).

We're moving away from measuring the tumor and counting the number of positive nodes and looking more closely at how the tumor is wired. If it's wired as HER2-positive, it is likely to be an aggressive tumor and should be treated as such. ■

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Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. **Abstract**

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

Slamon D et al. **Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study.** San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

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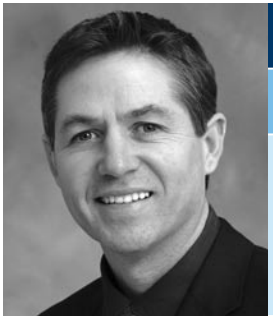

INTERVIEW

Paul E Goss, MD, PhD

Dr Goss is Professor of Medicine at Harvard Medical School, Director of the Breast Cancer Program at MGH Cancer Center, Co-director of the Breast Cancer Disease Program, DF/HCC and Avon Foundation Senior Scholar in Boston, Massachusetts.

Tracks 1-10

Select Excerpts from the Interview

Track 2

DR LOVE: What do we know about the impact of delayed endocrine therapy in postmenopausal patients with breast cancer who are five to 10 years out from their initial diagnosis?

DR GOSS: The Oxford overview has substantial and reliable data out to 15 years of follow-up, and in the MA17 trial, we have good data with postmenopausal patients who are five to eight years post-tamoxifen, so 12 to 13 years postdiagnosis. In the data, we see that this disease has a chronic relapsing nature that, by and large, doesn't lose its endocrine sensitivity.

DR LOVE: Should physicians be recommending adjuvant endocrine therapy to women years after diagnosis if they have not already received it?

DR GOSS: I believe that if you have a patient who never received adjuvant endocrine therapy or she received an abbreviated version or even if she has

completed standard endocrine therapy, you need to discuss delayed therapy with these patients.

DR LOVE: What is a patient's risk of relapse in that five- to 10-year window?

DR GOSS: For patients with node-positive breast cancer, it's four percent per annum. So between years five and 10, it's a 20 percent risk. For patients with node-negative disease, it's two percent per annum — in other words, 10 percent in those five years (Kennecke 2007).

Within those percents per annum, there are three types of recurrence — metastases, ipsilateral local recurrence and contralateral breast cancer — and the absolute benefit of therapy is reduced if the patient had a single or bilateral mastectomy.

However, in no patient is the level of risk of metastasis less than approximately 0.8 percent per annum, and the FDA approved tamoxifen for prevention of new primary breast cancer in women with a risk much lower than that — 0.3 percent per annum.

Why would we not consider delayed endocrine therapy for these patients? With metastases, not only is the risk higher, but it is a 0.8 percent per annum risk of death. Even in the patient at the lowest risk, the risk of death exceeds the risk of getting a new primary for patients that are FDA approved to receive tamoxifen.

Track 4

DR LOVE: What about adjuvant endocrine therapy for premenopausal patients?

DR GOSS: The questions of whether to perform an oophorectomy and whether to administer an aromatase inhibitor combined with ovarian suppression are still unanswered. In clinical practice, we are using the "old-fashioned" five years of tamoxifen in these patients. Both the TEXT and SOFT trials are addressing whether ovarian suppression in a premenopausal woman is advantageous, and I believe the answer will be yes.

Then the questions are, at what cost and in which patients? We know that bone loss is profound, and a paper recently published in *Neurology* suggests there may be a risk of dementia and Parkinsonism in the long-term follow-up of patients who have undergone premature oophorectomy (Rocca 2007a, 2007b).

That's not to say we wouldn't treat a woman at high risk in light of these risks, because you still have to consider her risk of dying from breast cancer.

Tracks 5-6

DR LOVE: What are the major unresolved issues relative to treating postmenopausal women with hormone-receptive breast cancer?

DR GOSS: Many issues are outstanding, such as the optimal duration of aromatase inhibitor therapy: Is the optimal duration 10 years or 15 years, or is it indefinite? If so, for which patients? What will be the cost? Which is the optimal agent?

One class study is comparing anastrozole versus exemestane, and a potency trial, the FACE study, is comparing letrozole to anastrozole.

Other issues include intermittent endocrine therapy and the idea of combining endocrine therapies, such as fulvestrant combined with an aromatase inhibitor.

DR LOVE: What about aromatase inhibitors and bone density?

DR GOSS: In 2006, I published two papers on aromatase inhibitors and bone health, in one of which I included a simple chart informing physicians exactly how to monitor patients with regard to bone health, how much calcium and how much vitamin D to recommend and which formulations are available for administration (Chien 2006; Perez 2006). ASCO also has a set of national guidelines.

If you follow the guidelines and monitor a patient's bone health appropriately, you need not alter what you're doing at all should she begin an aromatase inhibitor.

DR LOVE: Is a patient with a normal bone density at increased risk for fracture if she takes an aromatase inhibitor?

DR GOSS: In trials in which the patients were not properly monitored and treated, we noted an increased risk for fracture. However, now that we know more about the benefits of monitoring and salvage bisphosphonates, the answer is no. ■

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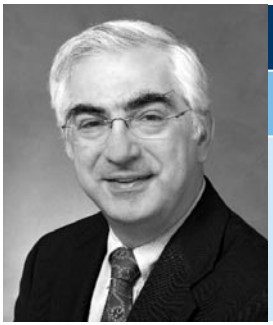

INTERVIEW

Thomas B Julian, MD

Dr Julian is Associate Professor of Human Oncology at Drexel University College of Medicine and Associate Director of the Breast Care Center at Allegheny General Hospital's Allegheny Cancer Center in Pittsburgh, Pennsylvania.

Tracks 1-9

Select Excerpts from the Interview

Track 2

DR LOVE: In which situations are you using MRI for patients who are not enrolled in a clinical trial?

DR JULIAN: We screen patients at high risk for breast cancer with MRI, and in that population of patients we have detected a few with breast cancer that were not identified by mammogram.

These are individuals who have a significant family history of first- and second-degree relatives with breast cancer and carriers for the BRCA1 and BRCA2 gene. Most of the time, these are individuals with a dense breast as determined by mammography.

The other group of patients in whom we're utilizing MRI are those with newly diagnosed cancer and a fairly dense breast. They may be premenopausal, perimenopausal or postmenopausal and treated with hormone therapy, which affects the density of the tissue. We evaluate the MRI to determine the extent of the disease and to provide a better approximation of the size of the tumor.

We're also using MRI in the neoadjuvant setting for patients with large tumors who would like to have a breast-conserving procedure. We evaluate the breast with an MRI to determine the tumor size, then administer neoadjuvant chemotherapy and follow a sequence to ensure that there is a reduction in the tumor size.

Ultimately, MRI aids in the final surgical planning if you're going to perform breast-conserving surgery. A complete clinical response is a great finding on the MRI. Unfortunately, I don't believe there's been enough information to equate a complete clinical response on an MRI with a complete pathologic response.

Tracks 4-5

DR LOVE: How do patients respond to the NSABP-B-42 trial, which is evaluating whether an adjuvant aromatase inhibitor should be continued beyond five years?

DR JULIAN: It's a bit of a mix because you have two groups of patients. One group says, "I have no problem being on the antihormonal therapy for five years, but I don't want to continue taking a pill." Those patients will not be excited about NSABP-B-42.

The other group of patients says, "I'm worried. I've been on this therapy for five years. How do I know that I am going to do as well if you take me off of it?" Obviously the answer is, "We don't have a good handle on that." We know historically from the tamoxifen trial that the outcomes were no better with 10 years versus five years (Fisher 2001). With the aromatase inhibitors, there may or may not be an advantage.

The problem we're faced with is the potential for side effects of the aromatase inhibitor for the additional period of time. However, a number of patients do not feel comfortable coming off of the aromatase inhibitor at five years. They view it as a security blanket.

I believe the NSABP-B-42 results are going to be important. If there is a major benefit to continuing the aromatase inhibitor for 10 years, then the patients need to know that to make an informed decision. If there is no benefit, we can save the patients from the side effects. ■

SELECT PUBLICATIONS

Boccardo F et al; Intergroup Exemestane Study. **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: Preliminary results of the Italian Tamoxifen Anastrozole Trial.** *J Clin Oncol* 2005;23(22):5138-47. **Abstract**

Fisher B et al. **Five versus more than five years of tamoxifen for lymph node-negative breast cancer: Updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial.** *J Natl Cancer Inst* 2001;93(9):684-90. **Abstract**

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005;97(17):1262-71. **Abstract**

INTERVIEW

Daniel F Hayes, MD

Dr Hayes is Professor of Internal Medicine and Clinical Director of the Breast Oncology Program in the Division of Hematology/Oncology of the University of Michigan Comprehensive Cancer Center's Department of Internal Medicine in Ann Arbor, Michigan.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: You've had a major leadership role in studying markers of prognosis and response to treatment. Where do you see the Onco*type* DX assay fitting into clinical practice?

DR HAYES: Our diagnostic skills and capabilities are primitive right now. We know that 80 to 85 percent of node-negative patients will never experience disease recurrence after surgery and radiation therapy no matter what we do, especially if they have ER-positive disease and receive endocrine therapy. Yet many of those women are also administered chemotherapy because we want to make sure we see the mortality reductions we believe are derived from adjuvant chemotherapy in those patients who do benefit.

There are women with node-negative disease who will experience a recurrence and would have benefited from chemotherapy. However, we don't know who they are. I believe the days of using anatomic prognostic factors are coming to an end. Biological factors have been used for many years, ever since Jensen and McGuire told us about ER (Horwitz 1978) and Slamon told us about HER2 (Slamon 1987).

What we need to do is get smarter about identifying the patients who have a high chance of recurrence and a high chance of benefiting, not just from chemotherapy but from specific types of chemotherapies. I'm optimistic we can do this.

In addition to ER, PR and HER2, we have had an enormous explosion in molecular biology. Now we have the ability to look at not just expression of multiple genes, but also at abnormalities in multiple genes at once — not just genes that are present in the tumor, but also genes that we inherit, which may ultimately affect how our cancers behave or how we behave when we're exposed to therapies.

I believe Onco*type* DX is a good assay. The developers and the investigators with whom they've collaborated have done all the things I would ask them to do to develop a new assay. They started out by asking, "What's the question?"

The question for many of us is about this group of patients — those with node-negative, ER-positive disease. If we assume they'll all receive hormone therapy, the question is, "Which of those patients still has a high risk of recurrence?" More importantly, "In which of those patients is chemotherapy likely to be of benefit?"

Track 6

DR LOVE: How does tumor size fit into treatment decision-making for patients with node-negative tumors?

DR HAYES: I'm increasingly less enthusiastic about tumor size. Tumor size, to me, doesn't mean a lot biologically. I'm not sure what tumor size reflects in terms of the odds of the cancer being able to metastasize, other than perhaps the tumor was growing quickly and became big before you picked it up, or that the tumor's been there a long time. I believe the biology within the tumor is more important than size.

DR LOVE: What do we know about the Onco*type* DX assay in larger tumors?

DR HAYES: All we know is from what was in the NSABP data (Mamounas 2005). I can't document this, but I believe patients in the critical B-14 and B-20 trials evaluating Onco*type* DX tended to be those who had something that suggested to their doctor that they had a worse prognosis.

I was an active clinician just starting my practice in the days when B-14 and B-20 were launched. Most of us were skeptical that adjuvant systemic therapy

would be of much benefit in node-negative patients. So the only ones we encouraged to participate in those studies were those we perceived were not going to do well.

This is total speculation, but one would guess that the patients on those studies probably have a slightly worse prognosis than the patients who didn't get on those studies.

We can now estimate the odds of benefit from chemotherapy with relative certainty or the relative ability to be pretty accurate. We can run through the numbers and tell a patient that she would improve her chance of being disease-free by two percent or five percent or 10 percent.

Overall in this country, life-threatening complications occur in about one percent of patients who obtain standard chemotherapy in the adjuvant setting for breast cancer — whether that's infection, bleeding, a second malignancy such as leukemia or heart failure.

In my clinic, if a woman is otherwise healthy and I calculate that she has a five percent or more benefit, I recommend treatment. If it's one or two percent, I don't. If it's three to five percent, I don't know what to do.

Track 11

DR LOVE: What's your take on the cardiac risk associated with adjuvant trastuzumab-containing chemotherapy regimens?

DR HAYES: The studies have been remarkably consistent. Across the board, for patients who previously received an anthracycline, about a five percent incidence of cardiac dysfunction can be measured by external monitoring with a multiple-gated acquisition (MUGA) scan or echocardiogram. About a one percent incidence of symptomatic congestive heart failure is seen. About 75 percent of those, maybe higher, seem to be reversible when you stop the drug.

I tell my patients there's a five percent risk of having some dysfunction that you probably won't even know about, but there's a one percent incidence of being symptomatic.

The big fear is whether those patients who had the reduction in cardiac function might, in the long run, be at higher risk for long-term cardiac problems. It may be that when you stop the drug, the cardiac dysfunction goes away and they never have trouble again. We just don't know. ■

SELECT PUBLICATIONS

Horwitz KB et al. **Steroid receptor analyses of nine human breast cancer cell lines.** *Cancer Res* 1978;38(8):2434-7. **Abstract**

Mamounas E et al. **Association between the 21-gene recurrence score assay (RS) and risk of locoregional failure in node-negative, ER-positive breast cancer: Results from NSABP B-14 and NSABP B-20.** San Antonio Breast Cancer Symposium 2005;**Abstract 29**.

Slamon DJ et al. **Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene.** *Science* 1987;235(4785):177-82. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Breast cancer patients with node-positive, hormone receptor-positive, early breast cancer have an annual risk of recurrence between years five and 10 after receiving tamoxifen of _____.**
   a. Four percent
   b. Eight percent
   c. 10 percent
   d. 20 percent
2. **Which of the following is part of the eligibility for the ACOSOG-Z1031 Phase III trial for patients randomly assigned to neoadjuvant hormonal therapy?**
   a. Premenopausal
   b. Postmenopausal
   c. ER-negative tumor
3. **What is the primary endpoint for the NSABP-B-39 study?**
   a. Recurrence-free survival
   b. In-breast tumor recurrence (IBTR) as a first event
   c. Distant disease-free interval
4. **Data from the NCIC-MA17 trial suggest greater benefit for letrozole in patients with _____ breast cancer.**
   a. ER-positive, PR-positive
   b. ER-positive, PR-negative
   c. ER-negative, PR-positive
5. **Which of the following clinical trials are evaluating whether adjuvant ovarian suppression is advantageous for premenopausal patients with hormone receptor-positive, early breast cancer?**
   a. SOFT
   b. TEXT
   c. BCIRG 006
   d. Both a and b
6. **In women with HER2-positive breast cancer, randomized clinical trials have demonstrated about a _____ reduction in the risk of recurrence with adjuvant trastuzumab.**
   a. 75 percent
   b. 50 percent
   c. 25 percent
   d. None of the above
7. **According to the MA17 study, the risk for disease recurrence was significantly reduced among patients treated with an aromatase inhibitor following five years of adjuvant tamoxifen compared to those who received placebo following tamoxifen.**
   a. True
   b. False
8. **In the initial group of patients entering the NSABP and NCCTG adjuvant trastuzumab trials, discordance in HER2 test results between field and central laboratories was approximately _____.**
   a. Five percent
   b. 10 percent
   c. 20 percent
   d. 30 percent
9. **Patients with hormone receptor-positive, node-negative breast cancer and a(n) _____ recurrence score on the Onco*type* DX assay have a high likelihood of benefiting from adjuvant chemotherapy.**
   a. High
   b. Intermediate
   c. Low
   d. Both a and c
   e. None of the above
10. **In the second interim analysis of the BCIRG 006 adjuvant trastuzumab trial, no significant difference in disease-free survival was observed between docetaxel/carboplatin/trastuzumab (TCH) and AC followed by paclitaxel/trastuzumab (AC → TH), but TCH resulted in significantly more cardiotoxicity.**
    a. True
    b. False
11. **The major risk associated with trastuzumab is cardiotoxicity.**
    a. True
    b. False

Post-test answer key: 1a, 2b, 3b, 4a, 5d, 6b, 7a, 8c, 9a, 10b, 11a

EVALUATION FORM

Breast Cancer Update for Surgeons — Issue 3, 2007

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GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *BCU* for Surgeons address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer in order to incorporate these data into management strategies in adjuvant and neoadjuvant disease. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of aromatase inhibitors in the adjuvant and neoadjuvant settings and of switching to or sequencing aromatase inhibitors after tamoxifen . . . . . 5 4 3 2 1 N/A
- Develop an algorithm for ER and HER2 testing and implement a treatment plan for patients with HER2-positive breast cancer . . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer. . . . . 5 4 3 2 1 N/A
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about availability and applicability of emerging research data on sentinel lymph node biopsy. . . . . 5 4 3 2 1 N/A
- Discuss the risks and benefits of partial breast irradiation and the clinical trials evaluating this technique with appropriately selected patients. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Pat W Whitworth Jr, MD	5 4 3 2 1	5 4 3 2 1
Dennis J Slamon, MD, PhD	5 4 3 2 1	5 4 3 2 1
Paul E Goss, MD, PhD	5 4 3 2 1	5 4 3 2 1
Thomas B Julian, MD	5 4 3 2 1	5 4 3 2 1
Daniel F Hayes, MD	5 4 3 2 1	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 N/A
Related to my practice needs. . . . . 5 4 3 2 1 N/A
Will influence how I practice. . . . . 5 4 3 2 1 N/A
Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
Overall quality of material. . . . . 5 4 3 2 1 N/A
Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
Avoided commercial bias or influence. . . . . 5 4 3 2 1 N/A

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EVALUATION FORM

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Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: DrNeilLove@ResearchToPractice.com
For CME/CNE Information	Email: CE@ResearchToPractice.com

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