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Patterns of Care in Medical Oncology

Management of Breast Cancer in the Adjuvant and Metastatic Settings

Adjuvant Endocrine Therapy

Adjuvant Trastuzumab

Adjuvant Chemotherapy

Systemic Therapy for Metastatic Disease

Editor
Neil Love, MD

A Case Survey Comparing Practices of Breast Cancer Investigators and General Oncologists

CME Certified

FROM THE PUBLISHERS OF:

Breast Cancer® UPDATE · Colorectal Cancer™ UPDATE · Lung Cancer™ UPDATE · Prostate Cancer™ UPDATE · Renal Cell Cancer™ UPDATE

Management of Breast Cancer in the Adjuvant and Metastatic Settings

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Continuing Medical Education (CME) Information

STATEMENT OF NEED/TARGET AUDIENCE

It is important for practicing oncologists to be aware of similarities and differences between his or her practice patterns, those of others in community practice and those of breast cancer clinical investigators. It is also important for oncologists to recognize that heterogeneity exists in the oncology community, especially in clinical situations for which there is suboptimal research evidence.

This program focuses on the self-described practice patterns of randomly selected medical oncologists on a variety of key clinical issues in cancer. Also included are clinical investigator commentary and references addressing these issues. This CME program will provide medical oncologists with information on national cancer patterns of care to assist with the development of clinical management strategies.

GLOBAL LEARNING OBJECTIVES FOR THE *PATTERNS OF CARE* SERIES

- Compare and contrast management strategies of community oncologists and cancer research leaders for the treatment of breast cancer in the adjuvant and metastatic settings.
- Discuss cancer management issues for which relative agreement and heterogeneity exist in patterns of care.
- Counsel cancer patients about multiple acceptable treatment options when they exist.

PURPOSE OF THIS ISSUE

The purpose of this issue of *Patterns of Care* is to support these objectives by comparing the perspectives of 150 randomly selected community medical oncologists with 45 breast cancer specialists and to offer in-depth commentary from faculty regarding their practice patterns in the management of breast cancer.

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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 2.25 *AMA PRA Category 1 Credit(s)™*. 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 evaluation located in the back of this book or on our website **PatternsOfCare.com**. PowerPoint files of the graphics contained in this document can be downloaded at **PatternsOfCare.com**.

COMMERCIAL SUPPORT

This program is supported by education grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc, Roche Laboratories 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.

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DISCLOSURE INFORMATION

Financial disclosures for oncologists quoted in this issue may be found in the cited CME pieces and journal publications of origin.

COMMENTS IN THIS MONOGRAPH

To highlight the practice issues presented in this survey, a number of excerpts are included from CME publications and peer-reviewed journal articles. For financial disclosures of authors, please refer to the original publications. Audio programs from Research To Practice can be accessed at **BreastCancerUpdate.com**.

ABOUT THIS SURVEY

This survey was completed in May 2006 by 150 community-based medical oncologists and 45 oncologists who specialize in breast cancer management (see list on pages 4-5) in the United States. The community-based oncologists were randomly selected from a proprietary mail list utilized by Research To Practice for distribution of its CME programs, and the specialists included physicians who have participated in education programs with Research To Practice and others referred for this project.

Editor's Note: Can good old-fashioned capitalism solve the problem?

One of the most intriguing aspects of my unexpected career as audio co-pilot for medical oncologists as they motor their way to and from their offices is the number of thoughtful correspondences I receive from listeners. This past week provided a cornucopia of communication, and excerpts from my three favorites are listed below.

These commentaries are reminders of the potential for bias in continuing oncology education, and our group continuously develops safeguards to optimize the scientific credibility of our work.

However, as Dr Bonnem suggests, it is the private sector in partnership with "can do" clinical investigators and research groups that currently drives the war on cancer, particularly with the combination of recent governmental cutbacks in public-sector funding of cancer research and the glacier-like action of governmental agencies. Consider my proposed top-10 list (page 4) of the most important recent advances in breast cancer clinical research, and ask yourself the question, "How much of the funding for these advances came from the private versus the public sector?" (For a snapshot of how these and other research advances are being translated into clinical practice, consider the results of the enclosed national survey of 150 medical oncologists in private practice and 45 clinical investigators and practitioners specializing in breast cancer oncology.)

It is interesting that, whereas a great deal of the R&D that led to these important steps forward came from the private sector, in the long run, our tax dollars pay handsomely for this work as Medicare and other public reimbursement mechanisms ultimately foot a hefty bill for oncologic products.

Our CME group tries to stick to clinical science, and we generally leave the political discussions to ASCO and other appropriate entities. However, if this truly is a war on cancer and if our lives are at stake, then we need results now. If incentivizing the private sector with huge potential profits will lead me, 20 years from now, to being cured of prostate cancer with a nontoxic therapy instead of being tortured with androgen deprivation, then I say, "Do it!" Back up the trucks to the Treasury and offer multibillion-dollar awards for results — not promises.

If you have a better way to get it done, shoot me an email.

— Neil Love, MD
NLove@ResearchToPractice.net

Most of your experts are from the world of academia. I think you are missing an opportunity to access other experts in the research divisions of various biotech and pharmaceutical firms. There is, for instance, far more expertise within Genentech on Avastin and Herceptin than you will find in any one academician. There is more expertise on Thalidomide within Celgene than anywhere else and more expertise on Sutent within Pfizer than in the academic world, etc.

It is probably true that some of the physicians who work for such organizations may want to keep some things confidential. But this is no different than Dr Perez playing it close to the chest before the revelation of the Herceptin data. You always ask your various experts where they think things will be in five or 10 years. Some of them speculate and many quite frankly don't know. By contrast, the researchers within the pharmaceutical industry could probably answer that question with a great deal of robustness, as they often plan out their trial strategies years in advance and have the multimillion dollar budgets to actually implement them. In the academic world, an idea percolates for a year and then it takes another year for a protocol to be written and get the papal blessing from the NCI and maybe another three or five years for a trial to accrue. Thank you for providing the tapes; it is a very positive service to the community.

— Eric Bonnem, MD
Portsmouth, NH

The new breast cancer think tank program was the best CD ever. What a group! Arguments are great — that's what we listen for. I loved the way you force them to weigh in on difficult subjects and actually say what they really do in practice. These eggheads do second opinions all day and with their fellows, they disparage and pick on the management of patients by the doctors in "Timbuktu." I loved hearing Hudis say he uses Xeloda with Avastin. Imagine if one of the other docs was seeing the patients for a second opinion and didn't know Hudis had been treating her. He'd rip the doc. Great discussion. I sat in my driveway until it finished — keep up the good work.

— Scott A Tetreault, MD
Fort Myers, FL

Dr Love, you and your staff deserve a strong "at-a-boy" for the breast cancer "think tank" just released. The disagreements that the participants voiced (and their occasional agreement) reflect reality, and this roundtable format seems more balanced and less likely to have bias than your one-on-one interviews. The entire think tank issue was free of commercial bias in my opinion. Your pharma support should welcome this type of effort.

In the individual interview programs, when you ask opinion leaders how they use a specific test or drug, it can sound like a commercial. Of course we want to know, but this think tank format of interchange between opinion leaders themselves with you as moderator preserved your independence. It worked. Regarding ER assays, I lent my copy to our pathologists. They actually welcome the information.

— Russell Jones, MD
Chattanooga, TN

Editor's Top-10 List of Most Significant Recent Advances in Breast Cancer Clinical Research

1. Adjuvant trastuzumab
2. Adjuvant aromatase inhibitors (AIs)
3. Delayed AIs and information on the natural history of ER-positive and ER-negative breast cancer
4. Onco*type* DX™ assay; relationship between ER status and benefit of chemotherapy; quality-control issues in ER, PR and HER2 assays
5. Dose-dense adjuvant chemotherapy and other taxane-based regimens
6. US Oncology TC versus AC study; increased appreciation for long-term toxicity of anthracyclines
7. Capecitabine in metastatic disease; CALGB-49907 (capecitabine versus AC or CMF in "elderly" women)
8. Bevacizumab in metastatic disease; emerging data on mechanisms of action of bevacizumab and other anti-angiogenic agents
9. Safety data from large clinical trials that identify unusual complications such as increased risks for arterial and venous events and alterations in bone health
10. Emergence of novel biologic targets and agents such as lapatinib

FIGURE 1

Clinical Investigators Completing the Survey

Alan B Astrow, MD
Director, Division of Hematology/Oncology
Maimonides Medical Center
Brooklyn, New York

Kimberly L Blackwell MD
Assistant Professor of Medicine and Radiation Oncology
Duke University Medical Center
Durham, North Carolina

Joanne L Blum, MD, PhD
Director, Hereditary Cancer Risk Program and Research Site Leader
Baylor-Charles A Sammons Cancer Center
Dallas, Texas

Adam M Brufsky, MD, PhD
Associate Professor of Medicine
University of Pittsburgh
Member, University of Pittsburgh Cancer Institute
Director, Comprehensive Breast Cancer Center
Associate Division Chief
University of Pittsburgh, Department of Medicine
Division of Hematology/Oncology
Pittsburgh, Pennsylvania

Daniel R Budman, MD
Professor of Medicine
New York University School of Medicine
Don Monti Division of Oncology
North Shore University Hospital
Manhasset, New York

Howard A Burris III, MD
Director of Drug Development
Sarah Cannon Research Institute
Nashville, Tennessee

Harold J Burstein, MD, PhD
Assistant Professor of Medicine
Breast Oncology Center
Dana-Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts

Lisa A Carey MD
Assistant Professor, Hematology and Oncology
Clinical Research Program
Lineberger Comprehensive Cancer Center
University of North Carolina
Chapel Hill, North Carolina

Robert W Carlson, MD
Professor of Medicine
Division of Oncology and Stanford Medical Informatics
Stanford University Medical Center
Stanford, California

John Carpenter, MD
Professor of Medicine
Division of Hematology/Oncology
University of Alabama at Birmingham
Birmingham, Alabama

Jenny C Chang, MD
Associate Professor of Medicine
Breast Center at Baylor College of Medicine
Houston, Texas

Rowan T Chlebowski, MD, PhD
Professor of Medicine
David Geffen School of Medicine at UCLA
Chief, Medical Oncology
Harbor-UCLA Medical Center
Torrance, California

Ellen Chuang, MD
Assistant Professor of Medicine
Weill Cornell Breast Center
Division of Hematology and Medical Oncology
Weill Medical College of Cornell University
New York, New York

Matthew J Ellis, MB, PhD
Associate Professor of Medicine
Head, Section of Medical Oncology
Director, Breast Cancer Program
Co-Director, Translational and Clinical Research
Anheuser Busch Chair in Medical Oncology
Washington University School of Medicine
St Louis, Missouri

Carol J Fabian, MD
Professor of Medicine
Division of Clinical Oncology
Director, Breast Cancer Prevention Center
Kansas Masonic Cancer Research Chair
University of Kansas Medical Center
Kansas City, Kansas

Kevin R Fox, MD
Director, Rena Rowan Breast Center
Associate Professor of Medicine
University of Pennsylvania Cancer Center
Philadelphia, Pennsylvania

William J Gradishar, MD
Director, Breast Medical Oncology
Professor of Medicine
Robert H Lurie Comprehensive Cancer Center
Northwestern University
Feinberg School of Medicine
Chicago, Illinois

Generosa Grana, MD
Associate Professor of Medicine
UMDNJ/Robert Wood Johnson School of Medicine
Director, Breast Cancer Program
Cooper Hospital
Camden, New Jersey

Jennifer J Griggs, MD, MPH
Associate Professor of Medicine and Oncology and Community and Preventive Medicine
James P Wilmot Cancer Center
University of Rochester
Rochester, New York

Clifford Hudis, MD
Chief, Breast Cancer Medicine Service
Solid Tumor Division
Memorial Sloan-Kettering Cancer Center
New York, New York

Continued

FIGURE 1 (CONTINUED)

Clinical Investigators Completing the Survey

Peter A Kaufman, MD
Associate Professor of Medicine
Section of Hematology/Oncology
Dartmouth-Hitchcock Medical Center
Comprehensive Breast Care Program
Norris Cotton Cancer Center
Lebanon, New Hampshire

Allan Lipton, MD
Professor of Medicine and Microbiology
Pennsylvania State University College of Medicine
Chief, Division of Oncology
Milton S Hershey Medical Center
Pennsylvania State University
Hershey, Pennsylvania

Gershon Locker, MD
Kellogg Scanlon Chair of Oncology
Evanston Northwestern Healthcare
Professor of Medicine
Northwestern University
Feinberg School of Medicine
Evanston, Illinois

Charles L Loprinzi MD
Professor of Oncology
Mayo Clinic College of Medicine
Rochester, Minnesota

Silvana Martino, DO
Director of Breast Cancer,
The Angeles Clinic and Research Institute
Santa Monica, California

Michelle E Melisko, MD
Clinical Instructor of Medicine
UCSF Comprehensive Cancer Center
San Francisco, California

Kathy D Miller, MD
Sheila D Ward Scholar of Medicine
Associate Professor of Medicine
Department of Hematology/Oncology
Indiana University School of Medicine
Indianapolis, Indiana

Anne Moore, MD
Professor of Clinical Medicine
Weill-Cornell Medical College
Trustee of the New York Academy of Medicine
Attending Physician
New York Presbyterian Hospital
New York, New York

Hyman B Muss, MD
Professor of Medicine
University of Vermont College of Medicine and
Vermont Cancer Center
Burlington, Vermont

Ruth O'Regan, MD
Director, Clinical and Translational Breast Cancer
Research
Assistant Professor of Hematology/Oncology
Winship Cancer Institute
Atlanta, Georgia

Joyce O'Shaughnessy, MD
Co-Director, Breast Cancer Research Program
Baylor-Charles A Sammons Cancer Center
US Oncology
Dallas, Texas

Beth A Overmoyer, MD
Northwestern Connecticut Oncology and
Hematology LLT
Torrington, Connecticut

Leroy M Parker, MD
Associate Clinical Professor of Medicine
Dana-Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts

John E Pippen, MD
Baylor-Charles A Sammons Cancer Center
Texas Oncology
Dallas, Texas

Lajos Pusztai, MD, PhD
Associate Professor of Medicine
Department of Breast Medical Oncology
The University of Texas MD Anderson
Cancer Center
Houston, Texas

Hope Rugo, MD
Clinical Professor of Medicine
Carol Franc Buck Breast Care Center
Director, Breast Oncology Clinical Trials Program
University of California, San Francisco
Comprehensive Cancer Center
San Francisco, California

Lee Schwartzberg, MD
Medical Director, The West Clinic
Memphis, Tennessee

Michelle Shayne, MD
American Board of Internal Medicine
Senior Instructor of Medicine
University of Rochester, Strong Memorial Hospital
Rochester, New York

Vered Stearns, MD
Assistant Professor of Oncology
Breast Cancer Research Program
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins School of Medicine
Baltimore, Maryland

Maria Theodoulou, MD
Associate Attending Physician
Breast Cancer Medicine Service
Department of Medicine
Memorial Sloan-Kettering Cancer Center
New York, New York

Debasish Tripathy, MD
Professor of Internal Medicine
Director, Komen UT Southwestern Breast Cancer
Research Program
University of Texas Southwestern Medical Center
Dallas, Texas

Vicente Valero, MD
Professor of Medicine
The University of Texas MD Anderson Cancer
Center
Houston, Texas

Charles L Vogel, MD
Medical Director, Cancer Research Network Inc
Plantation, Florida

Victor G Vogel, MD
Director, Magee/University of Pittsburgh Cancer
Institute Breast Cancer Prevention Program
Magee-Womens Hospital
Professor of Medicine and Epidemiology
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Eric P Winer, MD
Director, Breast Oncology Center
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

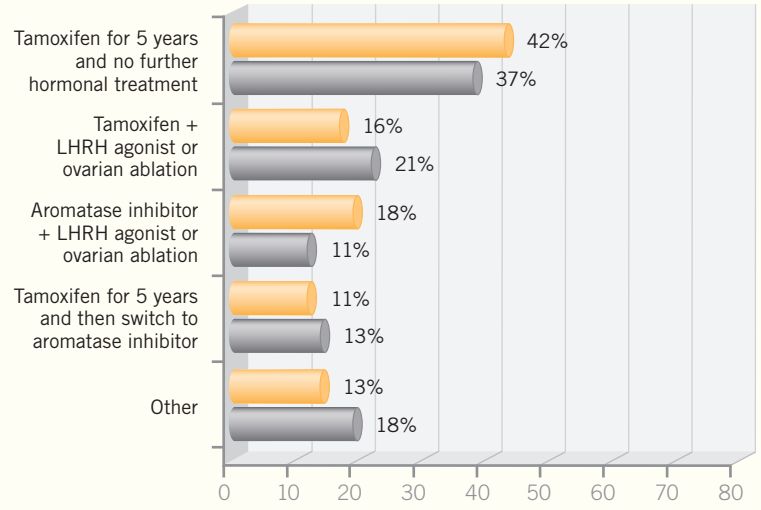
Adjuvant Endocrine Therapy

FIGURE 2

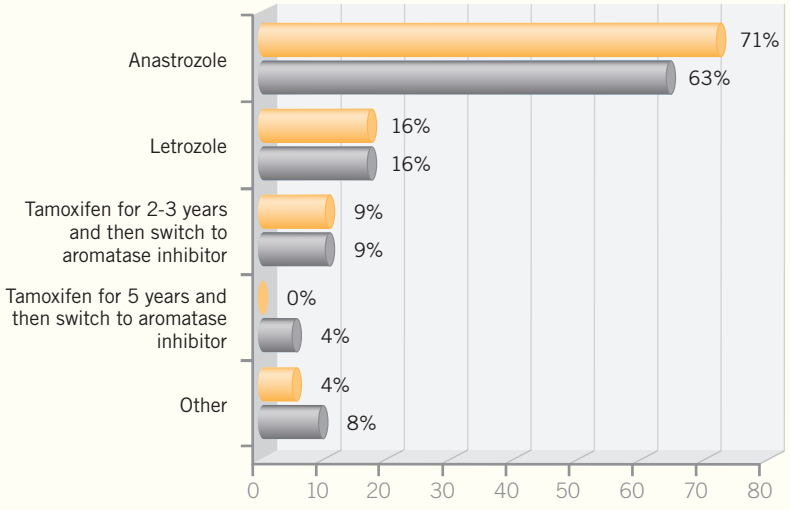
Which adjuvant endocrine therapy would you recommend initially for a woman with the following tumor?

- *1.2-centimeter, Grade II tumor*
- *ER 90%, PR 60%, HER2-negative*
- *3 positive nodes*

Age 35 (premenopausal with continued menses after chemotherapy)



Age 55 (postmenopausal)



Breast Cancer Update 2005 (8)

DR PETER M RAVDIN: I believe very few people are being started on tamoxifen with the intention of receiving five years of tamoxifen and then switching to an aromatase inhibitor.

The problem with initially starting on tamoxifen is that strategies that originally start with an aromatase inhibitor will have lower recurrence rates than those starting with tamoxifen.

If you start a patient on tamoxifen, you're conceding that she is going to do worse initially than she would have done on an aromatase inhibitor. Then you have to feel that when you switch her to an AI, the curves will then recross.

In other words, the aromatase inhibitor will be so much more effective if delivered later that it will catch up and overtake the group that did receive the aromatase inhibitor from the beginning.

That is possible, theoretically, because tamoxifen and the aromatase inhibitors have somewhat different mechanisms of action.

Therefore, a strategy that uses both agents might provide the most benefit. But that's a theoretical consideration against the very real fact that we know if you start with an aromatase inhibitor, the patients do better.

Breast Cancer Update 2006 (2)

DR KATHLEEN I PRITCHARD: When you consider randomized studies of up-front aromatase inhibitors in which disease recurs more in patients on tamoxifen than in those on the aromatase inhibitor in the first two years, it's difficult to suggest that you should begin with tamoxifen.

Until somebody shows in a randomized fashion that patients who begin with adjuvant tamoxifen are doing better at the end of five years than the patients who use an aromatase inhibitor initially, I will discuss with virtually all my postmenopausal patients the idea of beginning therapy with an aromatase inhibitor.

Breast Cancer Update 2006 (1)

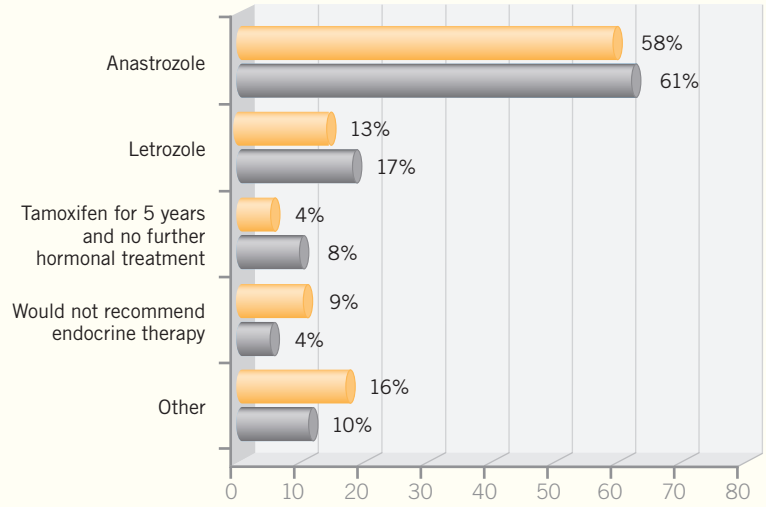
DR PAUL E GOSS: Two points for up-front therapy with an aromatase inhibitor are valid and worth discussing. The first one is that a slight balloon of events appears in the first 24 months among

FIGURE 2 (CONTINUED)

Which adjuvant endocrine therapy would you recommend initially for a woman with the following tumor?

- *1.2-centimeter, Grade II tumor*
- *ER 90%, PR 60%, HER2-negative*
- *3 positive nodes*

Age 85 (postmenopausal)



patients with receptor-positive breast cancer. Distant metastases, which are potentially fatal, occur in the first 24 months at a slightly higher rate than later.

The second point is that women treated with tamoxifen face a higher risk of side effects that are important, particularly gynecologic intervention, most of which is inappropriate. Gynecologists inappropriately intervene in the uterus for ultrasound-detected thickness that should be left alone. Nevertheless, the argument that's made is that an excess of events and toxicities makes the choice of tamoxifen in those initial two years inappropriate, and you should use an aromatase inhibitor up front.

The one thing that's consistent is that lowering estrogen with letrozole or anastrozole causes an enhanced bone resorption. The body tries to prevent that by compensating with bone formation, but the net result is bone loss and a decrease in bone mineral density (BMD).

That is a fact now, but there are a few caveats. Number one, all of this happened in an era during which most of the trials did not specifically recommend the appropriate osteoporosis guidelines for calcium and vitamin D supplementation, which is now being done widely.

Number two, women on aromatase inhibitors were not adequately screened with serial BMD tests, which are now being conducted.

Number three, bone loss very much depends on whether the woman took tamoxifen before the aromatase inhibitor because if she took tamoxifen before, her bone density is built up above the population average first and then taken down by the aromatase inhibitors.

If you look at MA17, for example, at time zero with five years of tamoxifen, bone density beats a population age-matched control. Over the next five years, it goes below the population age-matched control, but the net result is likely to be a return to square one. So it's not a massive clinical problem.

I don't want to understate it; it's a real issue, but we have tools to deal with it. In addition, now that we're monitoring more and can introduce the effective bisphosphonates that we know will counteract the aromatase inhibitors, I think we have a tight handle on this.

Breast Cancer Update 2006 (2)

DR ANTHONY HOWELL: All three aromatase inhibitors are showing about two to three percent bone loss per year, and we need to do something about that. What's interesting to us is that in the ATAC data, although the fracture rate was increased with anastrozole, it leveled off, and when the patient stopped treatment, the curves came right back together. If that's true, that's fantastic, but we need more data to confirm that.

I asked our bone specialists whether bone density can improve that quickly, and they pointed out that when steroids are stopped, bone reforms rapidly; they were not surprised by our findings.

Breast Cancer Update 2006 (2)

DR PRITCHARD: The absolute difference between the arthralgias in patients on aromatase inhibitors versus tamoxifen is about five percent. I believe the aches and pains that patients experience with aromatase inhibitors are real, but it's such a peculiar phenomenon.

Some of these women become miserable, and when you discontinue the drug, for many, the symptoms disappear. However, I've had some patients that I've put back on tamoxifen, and they still have the aches and pains.

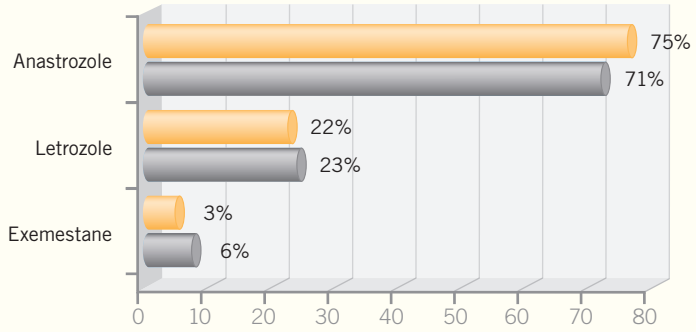
I think this side effect is related to the lowering of estrogen. Aches and pains are reported as a menopausal symptom and are generally regarded as not all that common or serious, but maybe we don't always listen to what women tell us about their menopausal symptoms.

With the aromatase inhibitors, we're seeing more osteoporosis. In the MA17 data, Goss showed more fractures and osteoporosis in the patients on the placebo arm of the original trial who crossed over to letrozole in the last

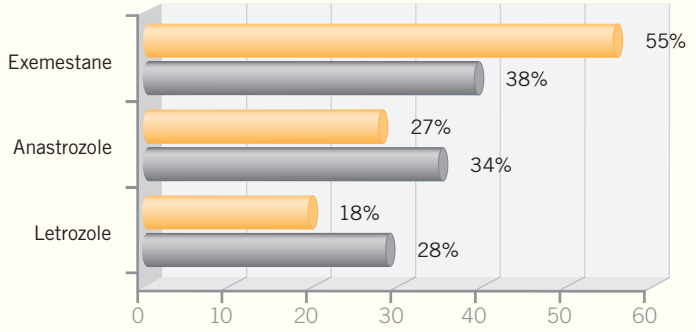
FIGURE 3

When you use an aromatase inhibitor for breast cancer patients in each of the following settings, which aromatase inhibitor do you generally utilize?

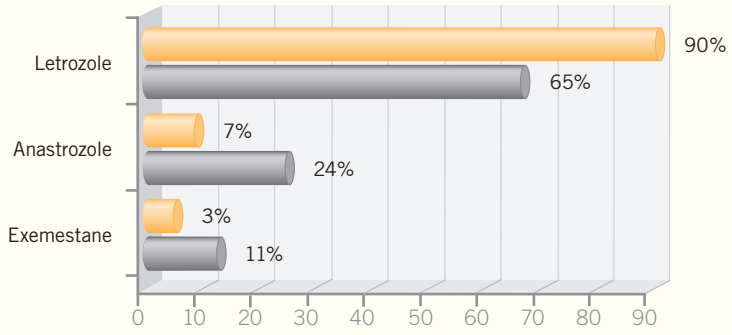
Initial adjuvant



Adjuvant after 2-3 years of tamoxifen



Adjuvant after 5 years of tamoxifen



two years after unblinding compared to those who did not.

I think we will see some long-term complications from this unless these patients are properly treated for their osteoporosis. We have to consider how well we are prepared to either treat our patients or collaborate with primary caregivers to prevent osteoporosis, which I think is not well managed in the general population.

Duffy S et al. The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: First results of the endometrial sub-protocol following 2 years of treatment. Hum Reprod 2006;21(2):545-53.

In summary, this sub-protocol has found fewer endometrial abnormalities arising de novo during 2 years of treatment with anastrozole compared with tamoxifen. This study also found that endometrial thickness, as a surrogate marker of endometrial proliferation, remained consistently <5 mm in the anastrozole group. In addition, there was less need for medical intervention.

Finally, the majority of endometrial abnormalities occurred in the first year of treatment. These findings are consistent with the superior safety profile and the lower risk of endometrial cancer with anastrozole compared with tamoxifen as demonstrated in the main ATAC trial.

Coleman RE et al. Effect of anastrozole on bone mineral density: 5-year results from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial. Proc ASCO 2006;Abstract 511.

Significant bone loss occurred throughout the five years in the anastrozole group, although there appeared to be a slowing down of the rate of bone loss in years two to five. Although no patients with normal BMD at baseline had become osteoporotic at five years, regular monitoring of BMD and bone protection strategies are likely to be required in patients receiving anastrozole in the presence of pre-existing osteopenia.

Breast Cancer Update 2006 (2)

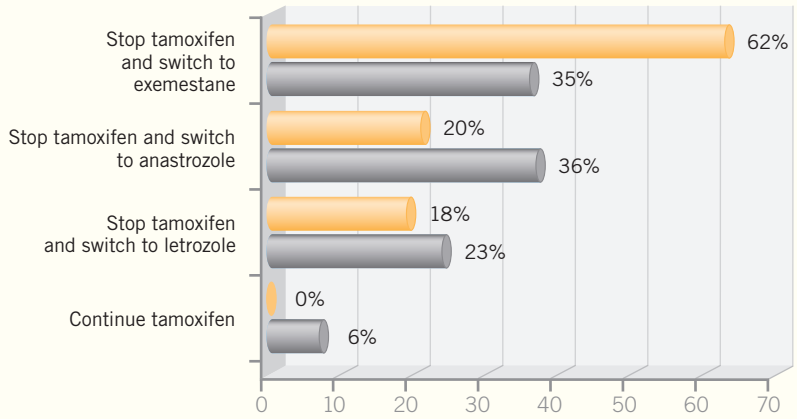
DR HOWELL: The San Antonio data from Jakesz are important because they show that the effect of switching is not quite as big as we once thought. Whereas the hazard ratio is approximately a 40 percent reduction in the switching studies, when they took into account the first two years, the reduction in the hazard ratio was about 24 percent.

Another significant finding was the survival advantage seen in the meta-analysis of the ARNO 95, ABCSG-8 and ITA trials. It was an impor-

FIGURE 4

How would you manage the therapy of this patient?

- *65-year-old woman in average health who has **completed 2 years** of tamoxifen*
- *1.2-centimeter, Grade II tumor*
- *ER-positive/PR-positive, HER2-negative*
- *3 positive nodes*



tant analysis because it showed, for the first time in an unselected population, the survival advantage of switching to anastrozole after two to three years of tamoxifen. Based on that, I feel we can use anastrozole in that clinical setting.

Paul Goss and Jim Ingle's papers also presented some beautiful data — although some of that is selected — demonstrating the efficacy of letrozole for patients with hormone receptor-positive breast cancer.

Combined, I believe these data highlight the importance of the aromatase inhibitors therapeutically. We've also seen that apart from the bone events and aching joints, aromatase inhibitors are better than tamoxifen as far as toxicity is concerned.

Robert NJ et al. Updated analysis of NCIC CTG MA.17 (letrozole vs placebo to letrozole vs placebo) post unblinding. Proc ASCO 2006;Abstract 550.

With 54 months follow-up the HR for DFS was 0.31 (0.18, 0.55: $p<0.0001$) favoring patients who crossed over to letrozole compared to those who stayed on no treatment. The treatment switch was well tolerated with no significant difference in bone fractures or cardiovascular events. ... Women with hormone dependent breast cancer prescribed letrozole after a prolonged delay from completing tamoxifen experienced a significant improvement in outcome (DFS, DDFS, OS) and should be considered for this therapy.

Kaufmann M et al. Survival benefit of switching to anastrozole after 2 years' treatment with tamoxifen versus continued tamoxifen therapy: The ARNO 95 study. Proc ASCO 2006;Abstract 547.

Median follow-up was 30.1 months. Switching to anastrozole significantly improved DFS and OS compared with continuing on tamoxifen. Fewer patients who switched to anastrozole reported serious adverse events (22.7%) compared with those who remained on tamoxifen (30.8%). ... Switching endocrine treatment improved DFS and OS in this well-defined population.

Postmenopausal women with hormone-sensitive EBC who have already received 2 years' adjuvant tamoxifen therapy should be switched to anastrozole.

Coombes RC et al. First mature analysis of the Intergroup Exemestane Study. Proc ASCO 2006;Abstract LBA527.

Switching postmenopausal patients with receptor-positive or unknown disease who remain disease free after two to three years of tamoxifen does appear to reduce the risk of dying — about a 15 to 17 percent reduction in the risk of death…serious side effects are rare, and many may in fact be attributable to tamoxifen withdrawal.

The switching strategy appears to minimize the adverse risks of both agents. Lastly, we conclude that with two to three years post treatment follow-up, the only disease related benefits previously reported appear to be maintained. We can conclude that exemestane is safe and well tolerated.

Breast Cancer Update 2006 (2)

DR RAVDIN: Paul Goss presented follow-up data on patients who participated in the Canadian trial comparing letrozole versus a placebo after completing five years of adjuvant tamoxifen. When they broke the code at two and a half years, some of the patients taking placebo decided to switch to letrozole and a few chose no further therapy. The patients who went on to take letrozole had much lower recurrence rates, although some of them had been off any endocrine therapy for four years.

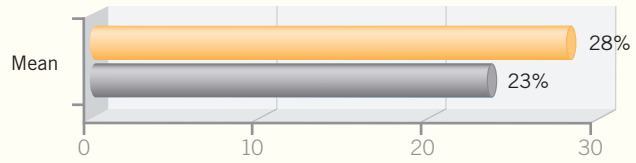
This analysis suggests that even years after stopping tamoxifen, patients can gain benefit from an aromatase inhibitor. In my practice, that means some of my patients, particularly the patients at high risk who have already been off tamoxifen for a year, should consider taking an aromatase inhibitor, specifically letrozole, because it's the only one that has been tested in this context.

Breast Cancer Update 2006 (1)

DR PRITCHARD: We're just starting to see women who have either received five years of an aromatase inhibitor, or who switched to an AI after two to three years of tamoxifen, and we don't know what to do in terms of continuing or stopping. I told the last patient I saw to continue

FIGURE 5

What percentage of your breast cancer patients on adjuvant aromatase inhibitors have significant arthralgias?



What percentage of your breast cancer patients on adjuvant aromatase inhibitors have significant arthralgias to the point that you consider discontinuing or switching agents?

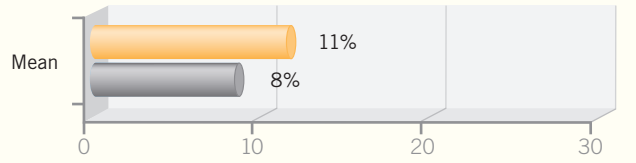
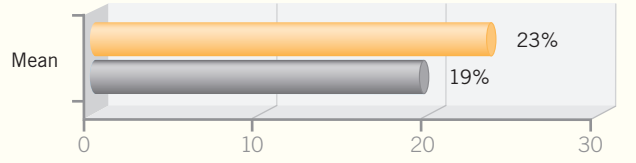


FIGURE 6

What percentage of the breast cancer patients you start on tamoxifen have significant vasomotor symptoms to the point that you consider interventions such as SSRI antidepressants?



her aromatase inhibitor and come back in six months because we would have a clinical trial for her. Both Jim Ingle and Paul Goss have presented data from the MA17 trial that suggest, year upon year, letrozole continues to add benefit.

However, until we see randomized studies, we're not going to know the best way to manage these cases. I think it's great that the NSABP is launching a study to evaluate patients who have had five years of any aromatase inhibitor or two or three years of tamoxifen followed by an aromatase inhibitor.

These patients will or will not then be randomly assigned to an additional five years of an aromatase inhibitor.

Breast Cancer Update 2006 (2)

DR RAVDIN: Aromatase inhibition probably should be continued indefinitely, and my opinion is based on two factors. One is that if a patient stops an aromatase inhibitor, her hormone levels will, of course, recover.

Second, it may be more difficult to develop resistance to estrogen deprivation than it is to develop resistance to tamoxifen. Tamoxifen is an agonist/antagonist, and preclinical work has shown that it can be reinterpreted as an estrogen by cancer cells, but I can't conceive of a pathway that would reinterpret no estrogen as an estrogen.

Breast Cancer Update for Surgeons 2006 (1)

DR J MICHAEL DIXON: In our preoperative study, we found the aromatase inhibitors were as effective at reducing proliferation in patients with HER2-positive disease as in those with HER2-negative disease. The degree of reduction was identical in patients with HER2-positive and HER2-negative disease. It's as though HER2 isn't important in relation to the likelihood of responding to an aromatase inhibitor.

Breast Cancer Update — Think Tank Issue 1, 2006

DR C KENT OSBORNE: One important issue is whether HER2 overexpression and PR loss predict for less benefit from tamoxifen than from an aromatase inhibitor. To me, the data are overwhelming that PR status predicts for response to tamoxifen.

In a prospectively designed SWOG trial published by Peter Ravdin, patients with metastatic disease were treated with tamoxifen. The trial was designed to address the value of PR status. On multivariate analysis, PR status was found to be an independent predictor. That was the first prospective trial following another five or 10 studies published in the early 1980s and late 1970s suggesting that patients with PR-negative disease responded less well to tamoxifen.

What about HER2 overexpression and tamoxifen? Most, but not all, studies show less benefit if HER2 is overexpressed. Preclinical studies strongly support the clinical data. So I tend to believe the majority of the clinical data, along with the biology, that HER2 does predict for less responsiveness to tamoxifen.

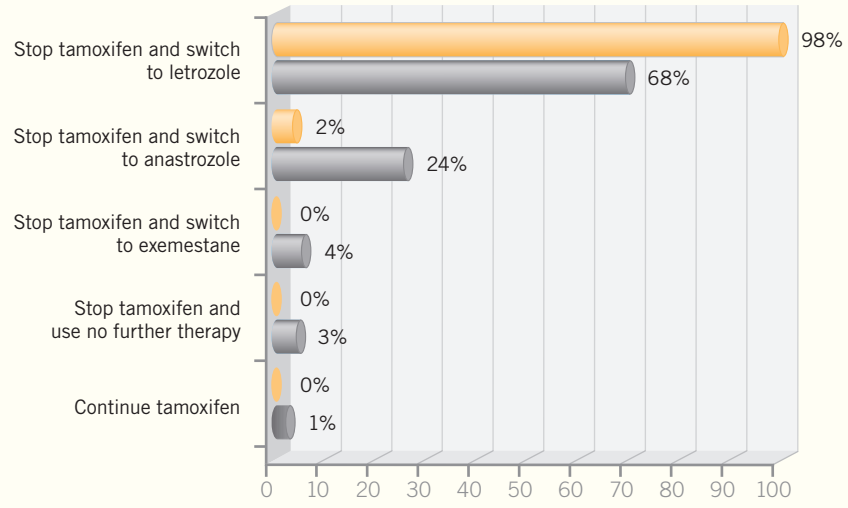
We have very little data with the aromatase inhibitors. We have three separate neoadjuvant trials and a fourth from Mike Dixon's group in Edinburgh that show very similar results. Whether it is letrozole or anastrozole, the responses are really quite good for patients with HER2-positive disease.

FIGURE 7

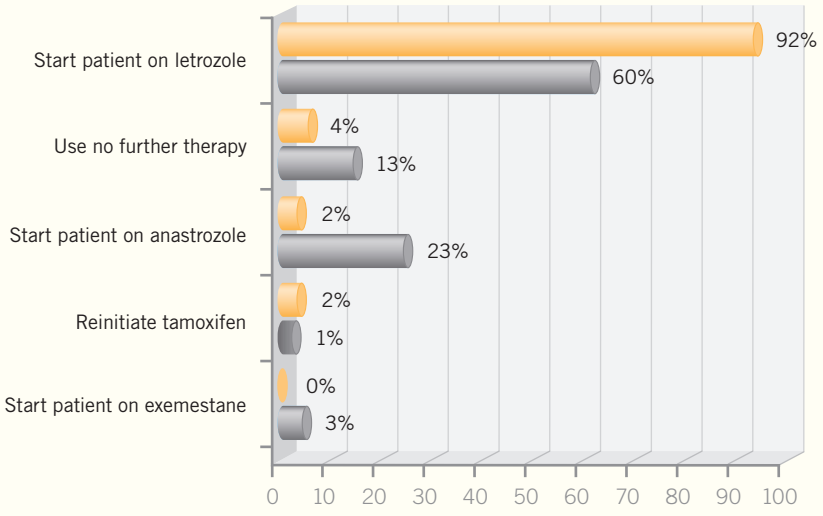
How would you manage the therapy at the following timepoints?

- *65-year-old woman in average health*
- *1.2-cm, Grade II tumor*
- *ER/PR-positive, HER2-negative*
- *3 positive nodes*

Has just completed five years of tamoxifen



Completed five years of tamoxifen one year ago



Breast Cancer Update — Think Tank Issue 1, 2006

DR GEORGE W SLEDGE JR: I find the ER-PR data interesting biologically. Having said that, I don't know how much real-world relevance it has because I can't pick out any population of patients in whom tamoxifen does better than an aromatase inhibitor.

Because of that, my default — unless it's going to be the oddball patient who can't tolerate an aromatase inhibitor for some reason — will be to use an aromatase inhibitor.

Breast Cancer Update 2006 (2)

DR MARTINE J PICCART-GEBHART: I tend to look at the profile of the tumor. If I'm dealing with a highly endocrine-responsive tumor with little worry about early relapse on therapy — a situation in which both ER and PR are very high, the proliferation genes are very low, the tumor is Grade I, and there is no HER2 overexpression — I believe there is a very low risk that the patient will relapse if you put her on tamoxifen for two years.

Breast Cancer Update 2006 (2)

DR RAVDIN: The ATAC trial found that the extra advantage of an aromatase inhibitor — in this case, anastrozole — was seen strongly only in the patients with ER-positive, PR-negative disease. This finding was based on 6,000 patients, and it had a very large *p*-value.

However, the BIG FEMTA study, which compared letrozole to tamoxifen as up-front therapy, did not find a significant difference in the efficacy of these agents relative to the status of the progesterone receptor.

The BIG investigators also evaluated the HER2 status of roughly 4,000 patients because data suggest that aromatase inhibitors may be more effective in tumors that are HER2-positive and ER-positive. They conducted a well-controlled study and found no significant difference on the basis of HER2, either.

The relationship between hormone receptor status and the impact of endocrine therapy was also examined in the NCIC-CTG MA17 trial. This trial randomly assigned patients who had taken five years of adjuvant tamoxifen to five years of letrozole versus a placebo. Patients with ER- and PR-positive disease particularly benefited from letrozole.

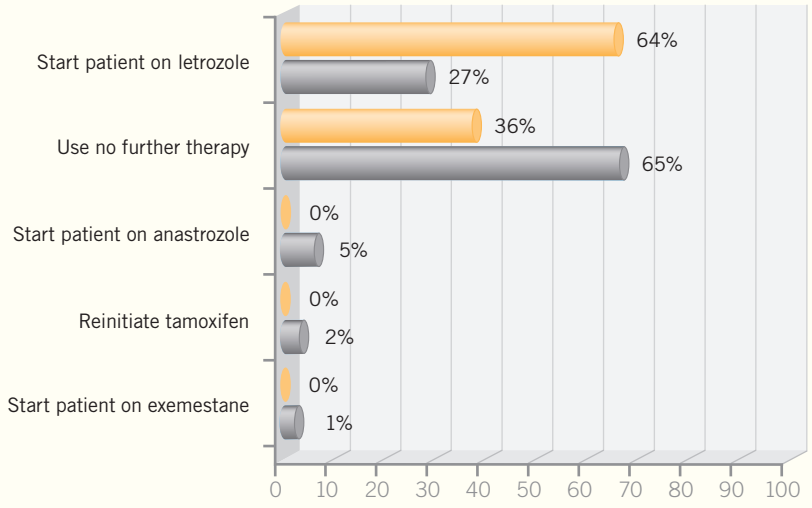
However, patients with ER-positive but PR-negative disease received no additional benefit from letrozole compared to tamoxifen. Interestingly enough, that observation is exactly opposite to that in

FIGURE 7 (CONTINUED)

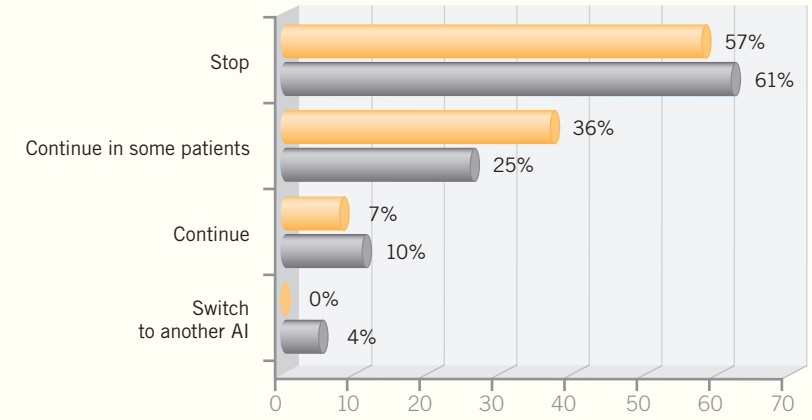
How would you manage the therapy at the following timepoints?

- *65-year-old woman in average health*
- *1.2-cm, Grade II tumor*
- *ER/PR-positive, HER2-negative*
- *3 positive nodes*

Completed five years of tamoxifen three years ago



How do you generally approach management of patients who have just completed five years of an AI?



the ATAC trial.

At this point, we have no way in clinical practice to specifically select patients, and in this state of uncertainty, an aromatase inhibitor is probably the better adjuvant endocrine therapy for postmenopausal patients with ER-positive breast cancer.

Dowsett M et al. Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status: An hypothesis-generating study. J Clin Oncol 2005;23(30):7512-7.

Retrospective subgroup analyses reported here showed that TTR was longer for anastrozole- than tamoxifen-treated patients in both the ER-positive/PgR-positive and the ER-positive/PgR-negative subgroups of patients, but the differential benefit was greater in ER-positive/PgR-negative tumors. These data are exploratory, should be considered hypothesis generating, and should be confirmed prospectively in other trials comparing the adjuvant use of an aromatase inhibitor with tamoxifen.

Breast Cancer Update 2006 (3)

DR KEVIN R FOX: If a premenopausal woman is treated with chemotherapy and becomes amenorrheic, it is inappropriate to assume that she will remain in a state of real menopause. Based on the natural history data, it appears to take two years to establish with some certainty that a woman will remain in a state of menopause.

If a 45-year-old woman — five years from the mean age of menopause — receives chemotherapy and becomes amenorrheic, I do not believe we can be assured that her ovaries will remain in a state of menopause until we've followed her for two years.

Breast Cancer Update 2006 (3)

DR FOX: The most significant challenge in developing new adjuvant strategies for premenopausal women with hormone receptor-positive breast cancers is the issue of ovarian suppression. We are participating in one of the two largest clinical trials addressing this issue: the SOFT trial, which randomly assigns premenopausal women with receptor-positive cancer to receive tamoxifen alone, ovarian suppression for five years with tamoxifen or ovarian suppression for five years with exemestane.

Breast Cancer Update 2006 (3)

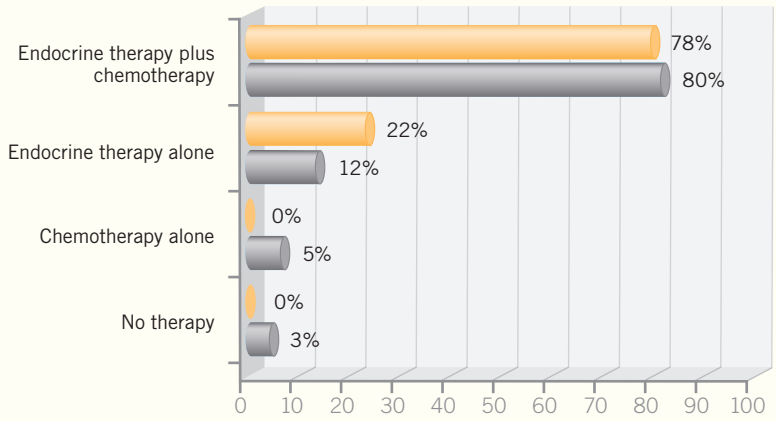
DR FOX: If our patients report two years of amenorrhea following adjuvant chemotherapy and we are considering switching them to an aromatase inhibitor, we always try to corroborate that

FIGURE 8

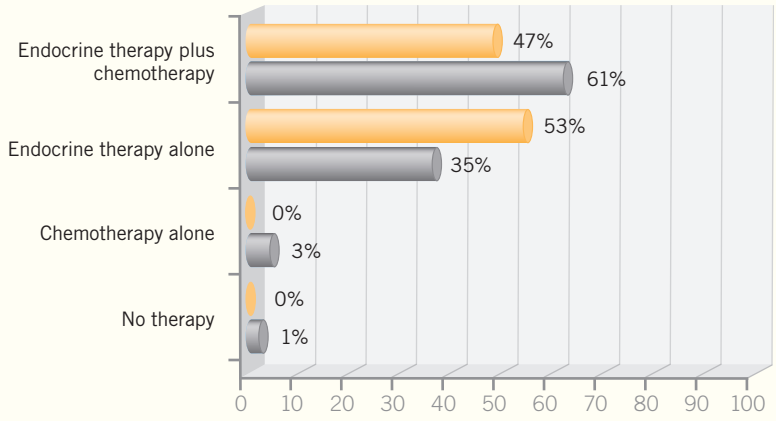
Which systemic therapy, if any, would you most likely recommend to a breast cancer patient with the following characteristics?

- *Average health*
- *1.2-centimeter, Grade II tumor*
- *ER/PR-positive*
- ***Negative nodes***

Age 35 (premenopausal)



Age 55 (postmenopausal)



information with an estradiol and an FSH level, recognizing the occasional shortcomings of either of those measurements. In my own practice, I require that a patient have nonmeasurable levels of estrogen and an elevated FSH level in the postmenopausal range before prescribing an aromatase inhibitor.

Breast Cancer Update — Think Tank Issue 1, 2006

DR ERIC P WINER: In premenopausal women with ER-positive disease, the issue of ovarian suppression with an aromatase inhibitor is being addressed in the SOFT and TEXT trials. At least some reason exists to be concerned that this could possibly be an inferior strategy.

In a woman who has a high level of estrogen in the premenopausal state, the estrogen levels go down after she receives ovarian suppression. Then adding an aromatase inhibitor and taking a woman down to extremely low levels of estrogen may add benefit.

It's also possible that taking those two steps down is, in fact, no better than a single step.

Of course, from a toxicity standpoint — as I think we're learning from both TEXT and SOFT — that deep plunge into not only menopause but menopause and an aromatase inhibitor is a pretty tough maneuver for most of these patients.

So for premenopausal women, I would strongly argue against using ovarian suppression and an aromatase inhibitor as an up-front strategy outside of a clinical trial.

What about the use of an aromatase inhibitor for a woman who is premenopausal at diagnosis, stops cycling soon after diagnosis and is now on tamoxifen for two years? This situation is much more analogous to the postmenopausal woman. She has now been without premenopausal levels of estrogen for two years. It is more likely that substituting an aromatase inhibitor for tamoxifen after two years could be of additional benefit.

We don't know that from any of the clinical trials that have been performed, but it seems more rational. However, we've all seen in practice — and Hal Burstein actually has a whole series of these women — patients who have been without menstrual cycles for a couple of years go off tamoxifen and start cycling again.

Breast Cancer Update — Think Tank Issue 1, 2006

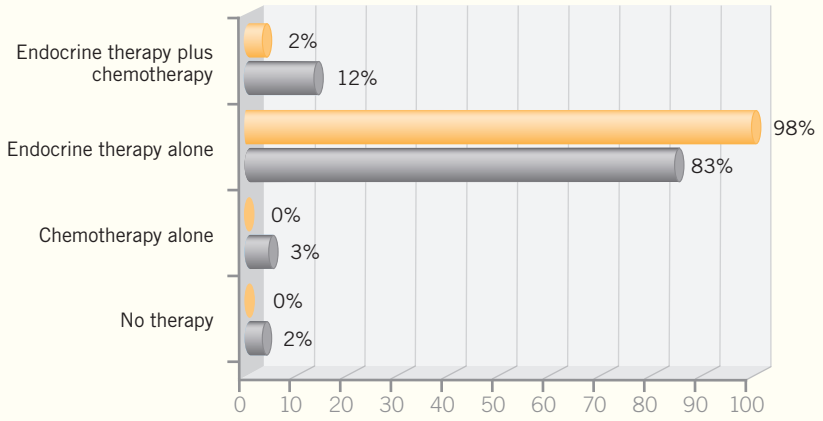
DR HAROLD J BURSTEIN: The point is made that amenorrhea is menopause, but that's not a very good definition for treating patients with aromatase inhibitors. We began to notice some patients — all of whom were women in their forties who had chemotherapy-induced amenorrhea — who were thought biochemi-

FIGURE 8 (CONTINUED)

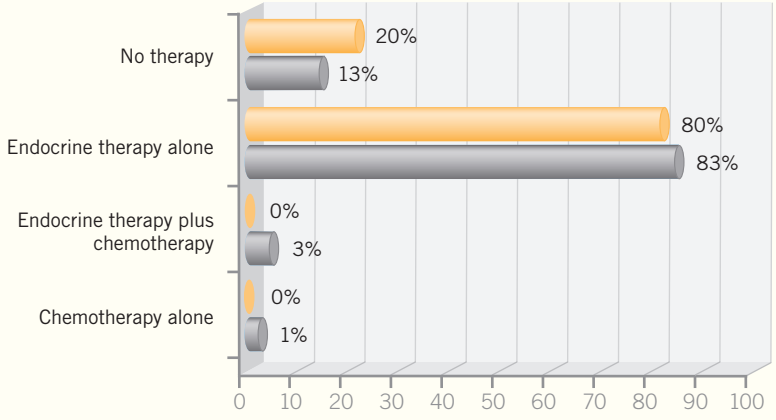
Which systemic therapy, if any, would you most likely recommend to a breast cancer patient with the following characteristics?

- *Average health*
- *1.2-centimeter, Grade II tumor*
- *ER/PR-positive*
- ***Negative nodes***

Age 75



Age 85



cally or on strong clinical grounds to be truly menopausal and were put on an aromatas.e inhibitor.

Usually, within six to 18 months they began to have menstruation again or had biochemical evidence of residual ovarian function, suggesting that they were not obtaining a therapeutic gain from an aromatase inhibitor.

Smith IE et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: Caution and suggested guidelines. J Clin Oncol 2006;24(16):2444-7.

Most women older than age 40 treated with chemotherapy will develop permanent amenorrhea. However, in a small minority, reported as 0% to 11%, ovarian suppression may be temporary, and they may renew menses over time. Our clinical observations suggest that the incidence of recovery is probably increased by the use of AIs (27% in our audit, compared with 0% to 11% spontaneously in women older than age 40).

Breast Cancer Update CME 2005

DR ROWAN T CHLEBOWSKI: The data you have to support using an LHRH agonist and an aromatase inhibitor for a younger woman at high risk with a HER2-positive tumor are a couple of Phase II trials in metastatic disease with fewer than 100 patients. So, in a certain sense, you have very limited information. Alternatively, you could administer ovarian suppression and tamoxifen.

That's what we've been doing. You deviate from these protocols in various ways. For women under 40 with hormone receptor-positive disease, we're routinely doing ovarian suppression with tamoxifen. We haven't utilized the combination of aromatase inhibitors with ovarian suppression yet. But I can see how it may not be an unreasonable extrapolation to do so.

Breast Cancer Update CME 2005

DR G THOMAS BUDD: Off protocol, in general, I use tamoxifen for premenopausal women. Whether ovarian ablation adds — in terms of efficacy — to chemotherapy or tamoxifen, I don't believe we know. We do know it adds toxicity.

That's what ECOG-E3193 in node-negative breast cancer showed. It's quite possible that it will end up adding efficacy, if we can select the right patient population, unconfounded by early menopause from chemotherapy.

Breast Cancer Update CME 2005

DR WILLIAM J GRADISHAR: The data we have available on ovarian suppression with tamoxifen or an aromatase inhibitor are still relatively limited. I would still view tamoxifen as the optimal therapy.

SELECT PUBLICATIONS

Baum M et al. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for**

FIGURE 9

Aromatase inhibitors as monotherapy are reasonable treatment options for actively menstruating patients.

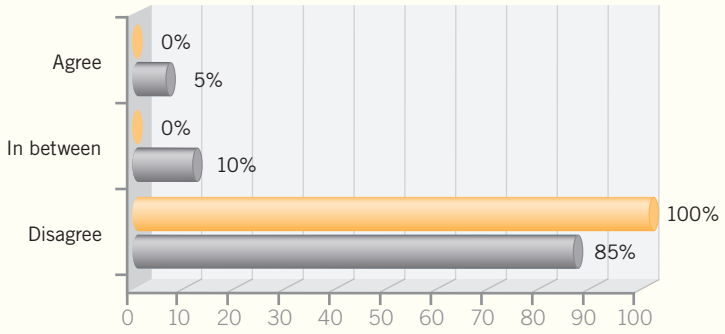


FIGURE 10

Does HER2 status influence your decision-making about utilizing an aromatase inhibitor in the adjuvant setting?

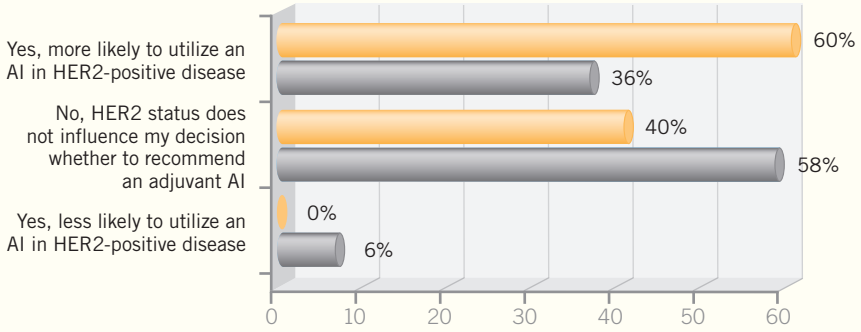
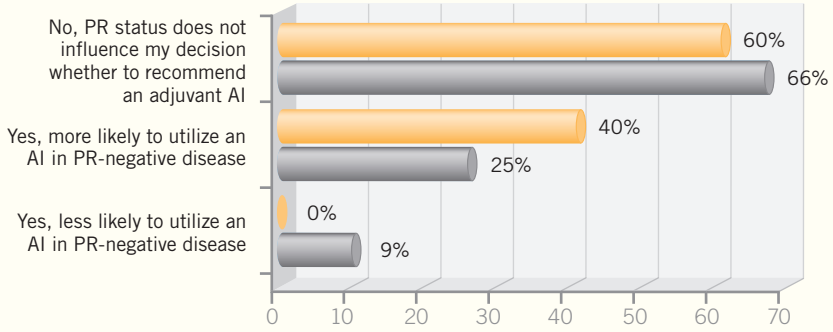


FIGURE 11

Does PR status influence your decision-making about utilizing an aromatase inhibitor in the adjuvant setting?



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

Bliss J et al. **First mature analysis of the Intergroup Exemestane Study.** Presentation. ASCO 2006;Abstract LBA 527.

Boccardo F et al. **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial.** *Ann Oncol* 2006;17(Suppl 7):vii10-vii14. Abstract

Boccardo F et al. **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

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

Duffy S et al. **The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: First results of the endometrial sub-protocol following 2 years of treatment.** *Hum Reprod* 2006;21(2):545-53. Abstract

Duffy S et al. **The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: Baseline endometrial sub-protocol data on the effectiveness of transvaginal ultrasonography and diagnostic hysteroscopy.** *Hum Reprod* 2005;20(1):294-301. Abstract

Howell A et al; ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. Abstract

Jakesz R et al; ABCSG and GABG. **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial.** *Lancet* 2005;366(9484):455-62. Abstract

Jonat W et al. **Switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-responsive early breast cancer: A meta-analysis of the ARNO 95 Trial, ABCSG Trial 8, and the ITA Trial.** San Antonio Breast Cancer Symposium 2005;Abstract 18.

Mincey BA et al. **Risk of cancer treatment-associated bone loss and fractures among women with breast cancer receiving aromatase inhibitors.** *Clin Breast Cancer* 2006;7(2):127-32. Abstract

Smith IE et al. **Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhea: Caution and suggested guidelines.** *J Clin Oncol* 2006;24(16):2444-7. Abstract

Thürlimann B et al; Breast International Group (BIG) 1-98 Collaborative Group. **A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer.** *N Engl J Med* 2005;353(26):2747-57. Abstract

Wasan KM et al. **The influence of letrozole on serum lipid concentrations in postmenopausal women with primary breast cancer who have completed 5 years of adjuvant tamoxifen (NCIC CTG MA.17L).** *Ann Oncol* 2005;16(5):707-15. Abstract

Adjuvant Trastuzumab

FIGURE 12

How many times have you started a breast cancer patient on adjuvant trastuzumab?

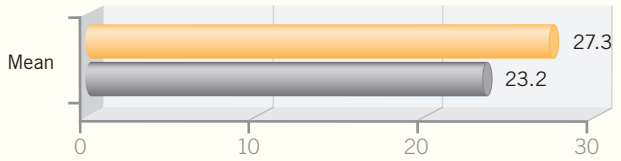
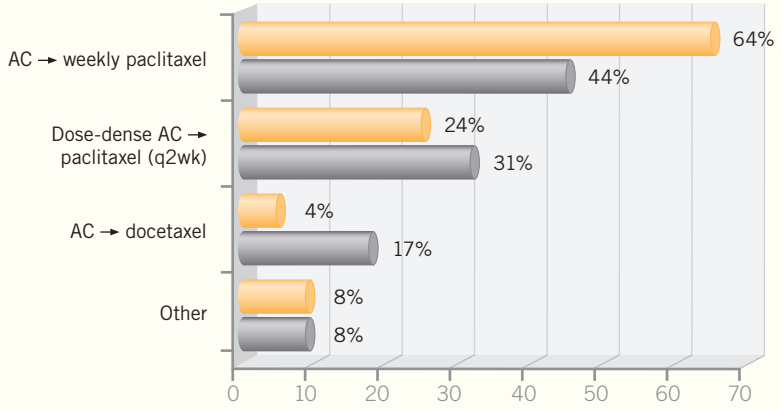


FIGURE 13

When utilizing adjuvant trastuzumab in breast cancer patients, what adjuvant chemotherapy regimen do you generally use?



Breast Cancer Update 2006 (3): Miami Breast Cancer Conference Tumor Panel Discussion

DR SLEDGE: Data from the HERA trial comparing observation versus one year of trastuzumab show a significant benefit in the addition of trastuzumab, with a risk reduction of about 50 percent and a strikingly positive *p*-value. It is interesting that this trial included no specified chemotherapy regimen and approximately one third of the patients had node-negative disease.

In contrast to the HERA trial, early analysis of the N9831 trial demonstrated that the result from the sequential arm, in which trastuzumab was administered after completion of chemotherapy, was not statistically significant, with a *p*-value of 0.01. From a purely statistical standpoint, this did not meet the boundaries required for early reporting.

The median follow-up in this trial is short, and the number of events is small, so which regimen is better is still an unanswered question. In the arm in which trastuzumab was administered concurrently with chemotherapy, the result was highly significant.

In the BCIRG 006 trial, both of the trastuzumab-containing arms were superior to the nontrastuzumab-containing arm. The nonanthracycline arm may be minimally inferior to the anthracycline-containing arm, but this is not yet a statistically significant difference and requires further follow-up.

If we examine all these trials as a group and include the FinHER trial, a small Finnish trial of adjuvant trastuzumab, in every single study we see significant benefits with the addition of trastuzumab to chemotherapy. As a result, trastuzumab has become the standard of care for patients receiving adjuvant therapy who have HER2-positive disease.

Breast Cancer Update: Special NSABP Edition 2005

DR NORMAN WOLMARK: The only test of concomitant versus sequential treatment with trastuzumab was from N9831, and when you evaluate the curves presented and the comparisons, one can't remain neutral. The concomitant arm (with paclitaxel) has a hazard rate that falls in line with what we're seeing in the other trials, whereas the sequential arm is, peer-wise, not statistically significant. It is not inappropriate for a medical oncologist to evaluate those data and be more impressed with concomitant therapy.

Breast Cancer Update: Special NSABP Edition 2005

DR DENNIS J SLAMON: The initial BCIRG 006 efficacy data are based on the first interim analysis of a three-arm trial with 300 events. We recognize that we're walking a fine line here, but still, both trastuzumab arms crossed their efficacy boundaries. The relevant question will be, how does the TCH arm, the nonanthracycline arm, look relative to the anthracycline-containing arm?

The risk reduction in the TCH arm is 0.39, and the risk reduction in the ACTH arm is 0.51 — almost identical to what was seen in the trials reported at ASCO for that type of combination. That's based on very few event differences between the two arms. We need to wait until the data mature, and it won't take a long time. Physicians should basically do what they feel most comfortable with at this point. If they feel more comfortable with the ACTH data, they should go with that arm, recognizing that those patients will have to be watched closely for cardiotoxicity.

FIGURE 14

Patients with HER2-positive, node-negative breast cancers less than 1 cm should generally receive adjuvant trastuzumab/chemotherapy as part of their treatment.

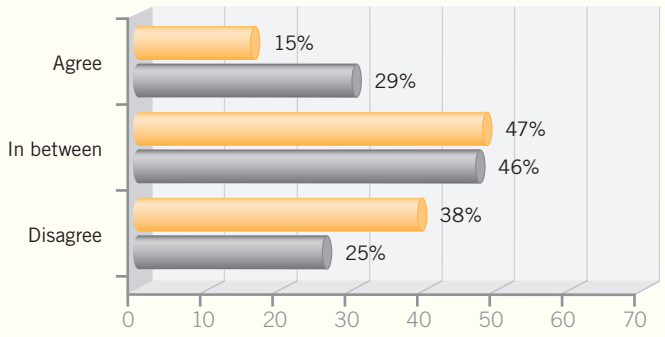
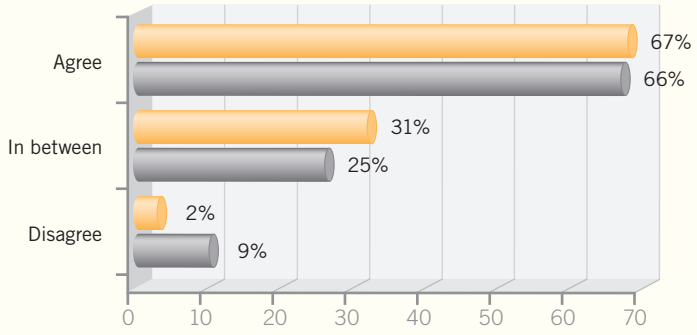
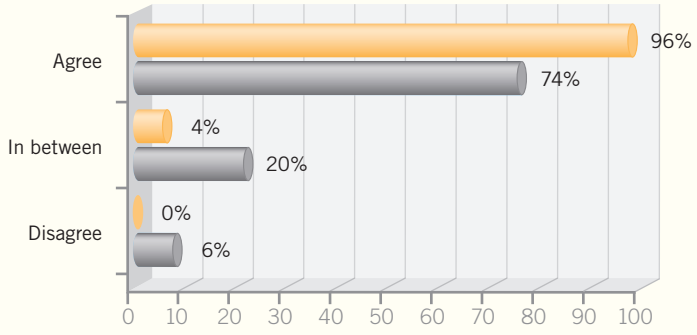


FIGURE 15

*Patients with **ER-positive,** HER2-positive, node-negative, 1-2-cm breast cancers should generally receive adjuvant trastuzumab/chemotherapy as part of their treatment.*



*Patients with **ER-negative,** HER2-positive, node-negative, 1-2-cm breast cancers should generally receive adjuvant trastuzumab/chemotherapy as part of their treatment.*



In terms of clinical chemotherapy-trastuzumab combinations, at this point we try, whenever possible, to avoid anthracycline-containing regimens because of the known interaction in terms of cardiac safety of trastuzumab with anthracyclines, and we're not restricted to TCH when using a nonanthracycline regimen. There are a number of different drugs that interact well with trastuzumab. However, we usually do use TCH in the adjuvant setting and will continue to do so until we see that it is inferior and the safety profile doesn't make up for that inferiority.

Breast Cancer Update 2006 (2)

DR BURSTEIN: The seminal question for the BCIRG 006 adjuvant trial was how the triplet — docetaxel, carboplatin and trastuzumab (TCH) — would compare with AC followed by docetaxel/trastuzumab and whether we could avoid using an anthracycline.

Although the numbers were not statistically significant, it struck me that there is still an advantage for the anthracycline-based chemotherapy. The trade-off that Dr Slamon reported is that there seems to be a slightly greater risk of cardiac toxicity for the women who received the anthracycline-based regimen but only about a one percent difference in terms of clinical cardiotoxicity events.

I think the findings from the TCH regimen are provocative, and we should continue to watch the data as they mature. However, for the moment I will continue to use AC followed by a taxane with trastuzumab as my principal adjuvant regimen for HER2-positive disease.

Breast Cancer Update 2006 (2)

DR JOHN MACKEY: The intent of the BCIRG 006 trial was to see if the preclinical synergy seen between docetaxel, carboplatin and trastuzumab would be borne out in the adjuvant setting and whether we could avoid major problems with cardiotoxicity by eliminating the anthracycline.

The trial demonstrated that both the ACTH arm and the novel arm of TCH outperformed the control arm, with haz-

FIGURE 16

Adjuvant trastuzumab should generally be started concurrently with chemotherapy rather than sequentially.

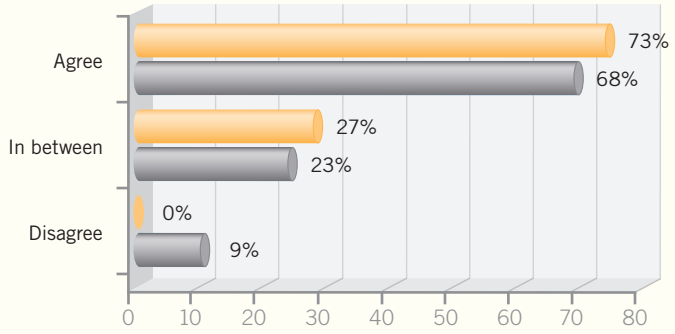
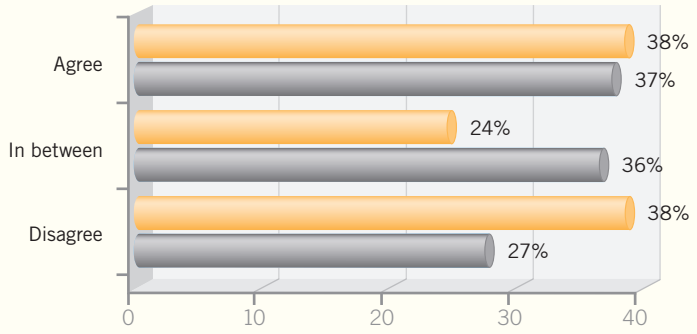


FIGURE 17

Trastuzumab monotherapy is a reasonable nonprotocol adjuvant treatment option in breast cancer patients who are unable to receive chemotherapy.



ard ratios of 0.49 and 0.61, respectively. No statistically significant difference appeared between the two experimental arms.

Interview, March 2006

DR CLIFFORD HUDIS: We are conducting a Phase II trial at Memorial with 70 patients treated with dose-dense AC/paclitaxel and trastuzumab. Our goal is to demonstrate a low or zero incidence of cardiac events, sufficient to convince us and the world that this regimen is safe. We are close to accomplishing that goal; however, the trial's not quite finished.

Now that we have evidence that dose-dense chemotherapy is a little bit better than conventional chemotherapy, we don't want to be in a position of choosing a less effective chemotherapy regimen when deciding to administer trastuzumab. That's the gap we're trying to close.

Breast Cancer Update 2006 (1)

DR PETER A KAUFMAN: We don't know the precise approach for the use of adjuvant trastuzumab in patients with node-negative disease, but any patient who meets the protocol-defined eligibility criteria is a reasonable patient for whom we should discuss the risks and benefits of trastuzumab.

I will caution that the number of patients with node-negative disease in our NCCTG-N9831 trial was modest — about 10 to 12 percent of the patients overall. So the findings are way too early for us to start looking at subsets, but I think trastuzumab is reasonable for patients who meet the criteria.

Meet The Professors 2005 (6)

DR WINER: I think the HERA results are impressive and stand on their own without a lot of difficulty. It is quite possible that concurrent may be better than sequential, but we don't know at the moment. The only reason we know anything from N9831 about sequential versus concurrent therapy is that when the DSMV met and decided to release the data about trastuzumab, as a practice management question in terms of what to tell doctors whose patients were on the trial, they asked to evaluate those two arms so that they could give doctors a sense of what to do for patients who had been treated on the trial and didn't receive trastuzumab.

Although there is a statistically significant difference between the concurrent and sequential arms on Edith's trial, and the sequential arm wasn't significantly better than no trastuzumab, it did not meet any boundary in terms of early stopping. We just need more data.

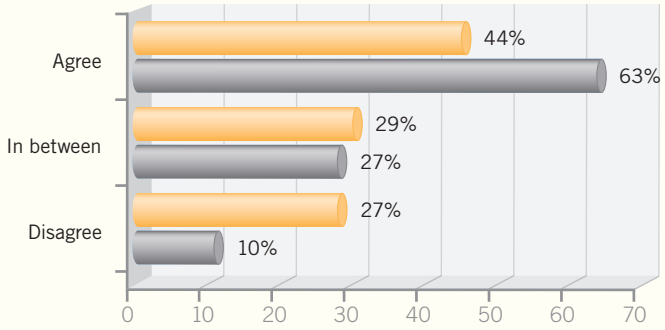
We know there's benefit from HERA. The risk reduction in HERA was similar to what we've seen in all of the studies. All of them — other than that one arm in N9831 — have shown that the use of trastuzumab either with or following chemotherapy reduces the risk of disease recurrence by about half, and the results are shockingly consistent.

Breast Cancer Update: Special NSABP Edition 2005

DR WOLMARK: I still have trepidation about using adjuvant trastuzumab in patients with node-negative disease and tumors of less than one centimeter. If the patient's tumor is ER-negative, the threshold to treat with trastuzumab is lower. However, for those with ER-positive disease, I would probably want to do an Onco*type* DX™ because I believe that is a reliable method to determine risk and would be helpful. If it's a high-risk

FIGURE 18

Dose-dense AC → paclitaxel/trastuzumab is a reasonable nonprotocol adjuvant treatment option for breast cancer patients with HER2-positive disease.



tumor, I would add trastuzumab to that regimen.

Breast Cancer Update 2006 (3): Miami Breast Cancer Conference Tumor Panel Discussion

DR JOYCE O'SHAUGHNESSY: If the tumor is greater than a centimeter in size and the patient has no contraindications to trastuzumab, I recommend it. For patients with tumors less than a centimeter, it depends on what I think their residual risk will be. For example, if a tumor is eight or nine millimeters but ER-negative and PR-negative, Grade III and HER2-positive by FISH, I recommend trastuzumab. For patients at higher risk, I always use AC followed by paclitaxel or docetaxel with trastuzumab, but for patients at lower risk, I consider TCH because it has less cardiac toxicity.

Breast Cancer Update 2006 (2)

DR PICCART-GEBHART: Women with HER2-positive tumors were allowed to enter the HERA trial if the tumor size was greater than one centimeter. This was the only criterion. We didn't require other aggressive features — it was purely based on pathological size.

Of course, now the problem we have is with young women coming to us with eight-millimeter tumors and negative nodes. Usually, when you look at the pathology, you see other features of aggressiveness — for example, a high proliferation rate, Grade III tumors and so on.

I don't see why these women would not derive a substantial benefit from trastuzumab. Provided these women are well informed about cardiotoxicity risk, we are discussing with them the possibility of trastuzumab.

Breast Cancer Update 2006 (2)

DR SANDRA M SWAIN: In NCCTG-N9831, about 10 percent of the patients had node-negative disease, and none of those patients had tumors that were less than a centimeter. Probably one of the questions I am asked the most right now is, "What do you do with a patient who has a three-millimeter, HER2-positive tumor?"

In BCIRG 006, about 30 percent of the patients had node-negative disease, and some of those patients did have very small tumors. There was not a size limitation, but it's still, again, limited in number. In the HERA trial, approximately 30 percent of the patients had node-negative disease. The HERA trial was very strongly positive for efficacy with sequential trastuzumab in the patients with node-negative disease.

Hence, strong data support the use of adjuvant trastuzumab in patients with node-negative disease. The nuances of its use are really about the tiny tumors.

The data indicate that a patient with a two- or three-millimeter tumor has an extremely good prognosis. I have not been recommending adjuvant trastuzumab for those very tiny tumors because of the risk of cardiac toxicity. It's not like tamoxifen, with which you have minimal risk. You do have risk, and it requires intravenous therapy for a year.

Breast Cancer Update 2006 (1)

DR KAUFMAN: We don't know whether women with a HER2-positive tumor smaller than one centimeter need adjuvant trastuzumab. We do need to be respectful of the fact that these women have a better prognosis because their tumors are so small. For women whose tumors are ER-positive and less than one centimeter, I've not offered trastuzumab.

For patients with ER-negative disease, I suppose one could consider trastuzumab, although the quantifiable gains from adding this agent are not known. It would be interesting to conduct a study evaluating trastuzumab with or without chemotherapy in patients with very small tumors.

Maybe we can begin to eliminate chemotherapy for the lower-risk patient population if we can alter the natural history of their disease. Data exist suggesting that trastuzumab may enhance the apoptotic function of a number of cytotoxic agents.

Dennis Slamon and Mark Pegram did much of the groundbreaking work demonstrating synergistic interactions between trastuzumab and a number of conventional cytotoxic agents that we use widely in breast cancer — docetaxel, paclitaxel and vinorelbine.

So if that preclinical finding was accurate, one would speculate or hypothesize that administering trastuzumab concurrently with cytotoxics might give you a much greater bang for your buck and much more clinical activity than waiting until the completion of chemotherapy to start trastuzumab.

In terms of the difference between sequential therapy versus no therapy with trastuzumab, we found in N9831 a 13 percent relative improvement in

FIGURE 19

Which therapy would you most likely recommend to a breast cancer patient with the following characteristics?

- *Woman in average health*
- *0.8-centimeter, Grade II tumor*
- *ER-negative/PR-negative, HER2-positive*
- *Negative nodes*

	Age 35		Age 55		Age 75		Age 85	
	CI*	CO†	CI	CO	CI	CO	CI	CO
Chemotherapy alone	18%	20%	22%	19%	9%	15%	—	8%
Chemotherapy plus trastuzumab	78%	68%	63%	60%	29%	27%	2%	9%
Trastuzumab alone	—	5%	2%	11%	9%	19%	11%	17%
No therapy	4%	7%	13%	10%	53%	39%	87%	66%

* CI = clinical investigators; † CO = community oncologists

FIGURE 20

If recommending trastuzumab, which duration of trastuzumab treatment would you use?

	Age 35		Age 55		Age 75		Age 85	
	CI	CO	CI	CO	CI	CO	CI	CO
6 months	—	6%	3%	5%	—	19%	—	28%
1 year	100%	84%	94%	89%	94%	78%	100%	69%
2 years	—	10%	—	6%	—	3%	—	—
Other	—	—	3%	—	6%	—	—	3%

FIGURE 21

If recommending trastuzumab plus chemotherapy, would you most likely start the trastuzumab during or after chemotherapy?

	Age 35		Age 55		Age 75		Age 85	
	CI	CO	CI	CO	CI	CO	CI	CO
During	86%	80%	82%	81%	85%	75%	—	71%
After	14%	20%	18%	19%	15%	25%	100%	29%

disease-free survival favoring sequential therapy that did not achieve statistical significance. Our data indicate a trend but not a definitive improvement or benefit with sequential therapy.

The HERA trial, which also looked at sequential therapy, did demonstrate a highly statistically significant improvement with the administration of trastuzumab in sequence with chemotherapy, after its completion.

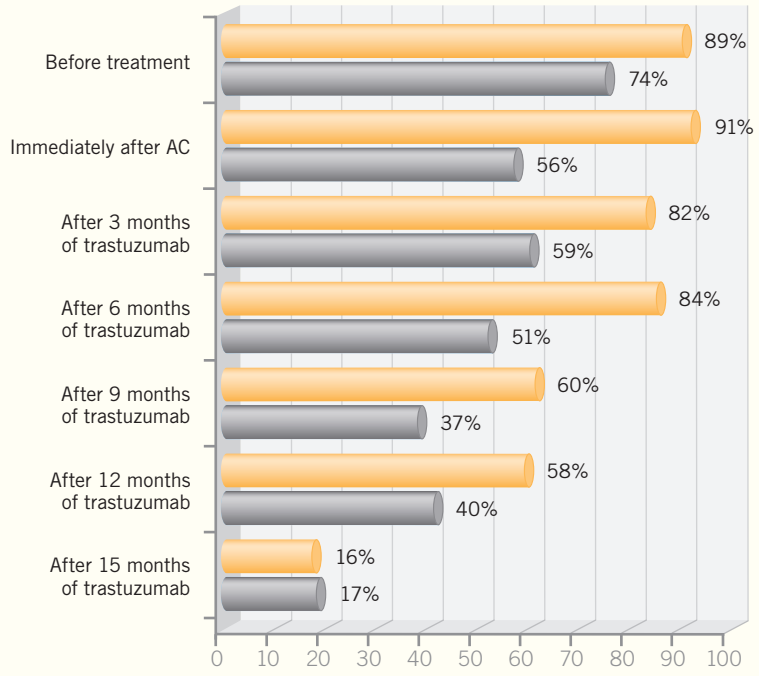
Time will tell. My prediction is that a benefit does exist with trastuzumab administered sequentially after the completion of chemotherapy. The HERA trial data are impressive, and it's a large study.

Meet The Professors 2006 (1)

DR HUDIS: I have not treated any patients with adjuvant trastuzumab monothera-

FIGURE 22

For patients who will be receiving adjuvant trastuzumab, when do you order MUGAs or ECHOs? (May have more than one response)



py, but if I'd ever be tempted, it would be for an older patient with a high degree of ER positivity. Data for such cases are desperately needed and would fill an important gap. Frankly, the remarkably consistent impact of trastuzumab raises the question of the contribution of the chemotherapy.

Breast Cancer Update 2006 (1)

DR SWAIN: I probably wouldn't use adjuvant trastuzumab without chemotherapy. Even if there's comorbidity, paclitaxel can be tolerated very well if you use it weekly.

Such a large amount of synergy data exists with trastuzumab, even though the HERA trial is positive with sequential use, I believe Dennis Slamon's laboratory data that indicate the synergy is important.

So I would try to use paclitaxel with trastuzumab in those patients, and if you're concerned about the anthracycline, just don't use that.

Breast Cancer Update 2006 (1)

DR CHARLES E GEYER JR: Right now, I would shy away from using adjuvant trastuzumab monotherapy, although it's easy to come up with scenarios where one would do that. The real rigid position is that we just don't know what trastuzumab does by itself or with hormonal therapy.

However, the magnitude of what we're seeing with adjuvant trastuzumab, particularly in the HERA trial on which it was administered by itself, makes it difficult to take that position.

If I have a patient who is older and I don't want to use TCH or doxorubicin, seeing the TCH data and knowing that weekly carboplatin and weekly paclitaxel are very well tolerated, I would be more inclined to make that sort of substitution.

If somebody is healthy enough that I want to provide her with the benefits of adjuvant trastuzumab, I would tend to recommend something like weekly carboplatin/paclitaxel rather than avoid chemotherapy altogether.

In terms of delayed trastuzumab, the HERA data suggest that trastuzumab as monotherapy beyond adjuvant treatment has a very low risk to it. So from the patient advocacy perspective, I see little downside to offering patients a year of trastuzumab if you know they have a substantial annual residual risk, which, for me, would be patients with node-positive disease.

The more difficult question is, how far out? I don't have an answer. It would be hard for me to justify it beyond five years. I think at that point patients have had enough time that they're likely to be beating the odds, so to speak.

It looks as though sequential AC followed by concurrent taxane/trastuzumab probably presents an increase in significant cardiac events of about three percent over baseline.

The cardiac events, as an endpoint in our study, meant that the patients died from cardiac causes or developed New York Heart Association Class III or IV heart failure. They experienced symptoms of heart failure with normal activity or at rest.

We will have to continue to follow the patients on these large adjuvant studies longer to obtain information regarding the long-term effects of trastuzumab after treatment is finished. NSABP-B-31 and NCCTG-N9831 were designed to check left ventricular function at 18 months, which was three months after trastuzumab ended and substantially longer from when the chemotherapy ended.

We are seeing encouraging results there, in that over time the slight decrements in ejection fraction across the groups diminish, and we do not see a great deal of difference looking at median ejection fractions. Even among the patients who did develop cardiotoxicity, in which their ejection fractions dropped to 30 percent or less, virtually all are up at least to 40 percent.

Recovery clearly occurs. It will take time to see what happens four and five years out. We also noted that relatively few new cardiac events are happening

beyond the end of trastuzumab treatment.

In BCIRG 006, they reported a 1.3 percent event rate with TCH versus 2.3 percent with AC followed by docetaxel/ trastuzumab. The difference was one percent.

The sequential AC taxane regimens have a cardiac event rate of about one percent. When you throw trastuzumab into that mix, you're probably adding on two or three percent.

I don't think there's a big difference between these numbers in terms of the absolute rate. I don't think that AC paclitaxel/trastuzumab is more cardiotoxic than AC docetaxel/ trastuzumab. We reported four percent; they reported two percent, but these are different trials.

Cardiotoxicity with TCH is less; they reported an incidence of 1.3 percent. In the HERA trial with trastuzumab by itself following doxorubicin, it was 0.5 percent. It's interesting to see the TCH at the level of the ACT — both of them higher than what HERA was reporting.

It's always problematic to compare absolute numbers across protocols, but the HERA number was strikingly the lowest number. If you want safety to be your dominant concern, then the HERA regimen seems, based on the data, to be the safest.

Breast Cancer Update 2006 (1)

DR GEYER: When we performed our cardiac safety analysis, we looked for predictors of the cardiac events. The things that held up in multivariate analysis were the age going in and the post-AC LVEF. For instance, patients 50 years old and older who had a post-AC ejection fraction of 50 to 54 percent had a cardiac event rate of 20 percent in our study. The lower boundary of that confidence interval was 11 percent, so that's a very high number.

Based on our data and what I've seen, I think the post-AC ejection fraction provides an extra measure of safety, coupled with the fact that it does seem as if no matter how trastuzumab is administered, it provides substantial benefits. So if I can do that and minimize toxicity, to me, that's important.

Slamon D et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. SABCS 2005;Abstract 1.

With over 23 months of follow-up, the primary endpoint of disease-free survival in both experimental arms of BCIRG 006 was achieved. The secondary endpoint of overall survival is not yet mature enough to report differences.

The cardiac safety data show a statistically significant higher instance of cardiac events in the ACTH arm compared to either the ACT or the TCH arm, but also importantly, there are persistent LVF declines in the anthracycline-containing Herceptin arm compared to the non-anthracycline Herceptin arm TCH.

For the global safety, they were tolerated well. Nonhematologic toxicity was evenly distributed, and all three regimens were well tolerated. The final observations are that the LV declines sustained with ACT and ACTH do last up to 550 days at the point of the last follow-up for a significant number of these patients.

Coamplification of the TOPO II gene with HER2 may identify a subset of the HER2-amplified that might benefit from anthracycline, making it worth the risk of cardiac dysfunction. Conversely, 65 percent of the patients do not have TOPO II amplification, and they may be ideal candidates for an efficacious nonanthracycline-containing regimen.

Smith I, on behalf of the HERA Study Team. Trastuzumab following adjuvant chemotherapy in HER2-positive early breast cancer (HERA trial): Disease-free and overall survival after 2 year median follow-up. ASCO 2006.

In conclusion, trastuzumab following adjuvant chemotherapy significantly improves overall survival among women with HER2-positive breast cancer. The disease-free survival gain reported after the one-year median follow-up is maintained after two years' median follow-up, and the risk of cardiotoxicity remains low.

Long-term follow-up will provide continuing safety data, important information on duration of trastuzumab treatment — one year versus two years — and, perhaps, information on the effect of delayed switching to trastuzumab in the observation arm.

SELECT PUBLICATIONS

Dang C et al. **Updated cardiac safety results of dose-dense (DD) doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) with trastuzumab (H) in HER2/neu overexpressed/amplified breast cancer (BCA).** *Proc ASCO* 2006;**Abstract 582**.

HERA Study Team. **Trastuzumab (H: Herceptin) following adjuvant chemotherapy (CT) significantly improves disease-free survival (DFS) in early breast cancer (BC) with HER2 overexpression: The HERA Trial.** San Antonio Breast Cancer Symposium 2005;**Abstract 11**.

Joensuu H et al; FinHer Study Investigators. **Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer.** *N Engl J Med* 2006;354(8):809-20. **Abstract**

Kim C et al. **Trastuzumab sensitivity of breast cancer with co-amplification of HER2 and cMYC suggests pro-apoptotic function of dysregulated cMYC in vivo.** San Antonio Breast Cancer Symposium 2005;**Abstract 46**.

Perez EA et al. **Interim cardiac safety analysis of NCCTG N9831 Intergroup adjuvant trastuzumab trial.** *Proc ASCO* 2005;**Abstract 556**.

Piccart-Gebhart MJ. **First results of the HERA trial.** Presentation. ASCO 2005. No abstract available

Piccart-Gebhart MJ et al; Herceptin Adjuvant (HERA) Trial Study Team. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. **Abstract**

Press MF et al. **Topoisomerase II-alpha gene amplification as a predictor of responsiveness to anthracycline-containing chemotherapy in the Cancer International Research Group 006 clinical trial of trastuzumab (herceptin) in the adjuvant setting.** San Antonio Breast Cancer Symposium 2005;**Abstract 1045**.

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

Romond EH et al. **Doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab as adjuvant therapy for patients with HER-2 positive operable breast cancer — Combined analysis of NSABP-B31/ NCCTG-N9831. Presentation.** ASCO 2005. No abstract available

Tan-Chiu E et al. **Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31.** *J Clin Oncol* 2005;23(31):7811-9. **Abstract**

FIGURE 23

*What percent of your breast cancer patients with **node-negative tumors** receiving adjuvant chemotherapy receive regimens that include taxanes?*

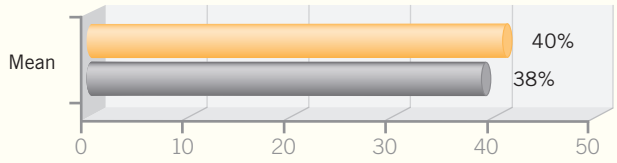
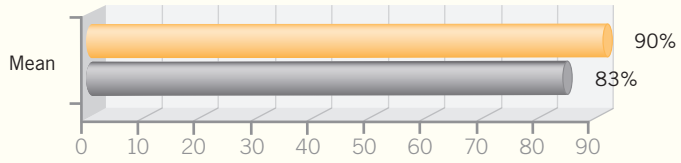


FIGURE 24

*What percent of your breast cancer patients with **node-positive tumors** receiving adjuvant chemotherapy receive regimens that include taxanes?*



Breast Cancer Update 2006 (2)

DR PICCART-GEBHART: I believe that in the not-too-distant future, we will approach the choice of chemotherapy completely differently. We used to think according to risk, dividing the choice of chemotherapy regimens into the most appropriate for patients with node-positive versus node-negative disease.

We are going to move away from that because we are entering an era in cancer medicine with the development of superb tools to predict which tumors respond to which drug.

We are not there yet, but this is going fast. The technologies are exploding. If we, the clinicians, are smart enough to design the right studies to validate these technologies quickly, it's going to change the picture.

Instead of our habit of thinking that six positive nodes means dose-dense chemotherapy, we should look at the profile of the tumor first. After that we can look at the nodes because the number of nodes is related to risk.

I would never administer dose-dense chemotherapy to a patient with a Grade I, highly endocrine-responsive tumor with maximum receptors and a very low proliferation index. On the contrary, if I see a young patient with negative nodes but an aggressive tumor with absolutely no endocrine receptors whatsoever, no HER2 and very high proliferation, I would be tempted to use dose-dense therapy.

Martin M et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352(22):2302-13.

In BCIRG 001, a randomized, phase 3 trial of adjuvant chemotherapy in women with operable node-positive breast cancer showed that, at a median follow-up of 55 months, the estimated rate of disease-free survival at 5 years was 75 percent in the TAC group and 68 percent in the FAC group ($P = 0.001$). The relative risk of death was 30 percent lower among women in the TAC group than among those in the FAC group.

Moreover, treatment with TAC, as compared with FAC, was associated with a 28 percent relative reduction in the risk of relapse. The reduction in the risk of relapse did not seem to be driven by nodal status or by hormone-receptor or HER2/neu status.

Perez E. TAC — A new standard in adjuvant therapy for breast cancer? N Engl J Med 2005;352(22):2346-8.

On the basis of the available data, one can consider TAC to be a standard of care, as is the dose-dense regimen of doxorubicin and cyclophosphamide followed by paclitaxel, for patients with resected node-positive breast cancer. However, the exclusion of patients older than 70 years and the toxic effects associated with TAC in the BCIRG trial cannot be minimized.

With this regimen, prophylactic growth-factor support is necessary to ameliorate myelosuppression and febrile neutropenia. A recommendation for the selection of one regimen over the other must await completion of the prospective National Surgical Adjuvant Breast and Bowel Project trial B-38, for which the accrual of data is expected to be complete in the next few years.

Seidman A. Current status of dose-dense chemotherapy for breast cancer. Cancer Chemother Pharmacol 2005;56(Suppl 7):78-83.

Dose-dense trials have demonstrated that filgrastim facilitated bi-weekly chemotherapy is feasible. Based on the landmark results of CALGB 9741, many groups have adopted this strategy as a new standard of care. However, appropriate caution should be applied in extrapolating these data to any/all regimens outside a clinical trial setting, since unanticipated toxicities may emerge.

At Memorial Sloan-Kettering Cancer Center (MSKCC) and elsewhere, feasibility trials are either planned or under way exploring dose-dense regimens con-

CLINICAL INVESTIGATORS COMMUNITY ONCOLOGISTS

FIGURE 25

*In general, when using chemotherapy in the adjuvant setting in patients with **smaller, node-negative, ER-positive, HER2-negative tumors**, what tends to be the most common regimen you utilize?*

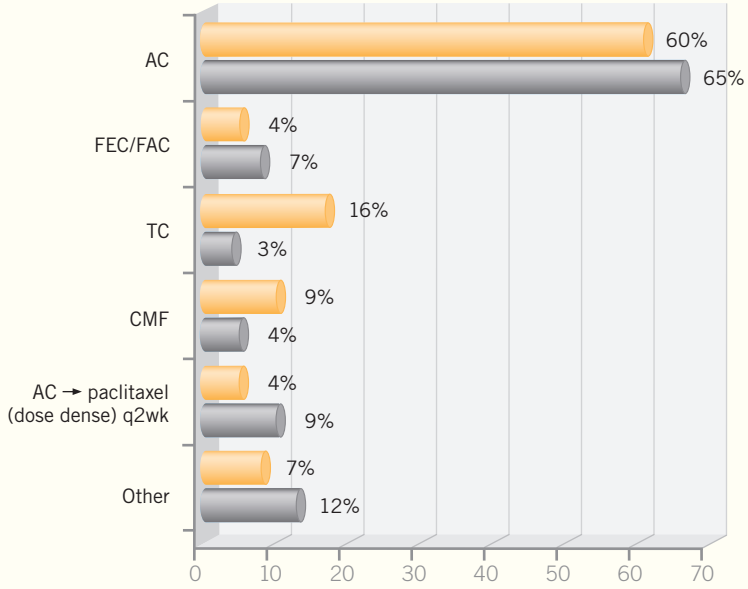
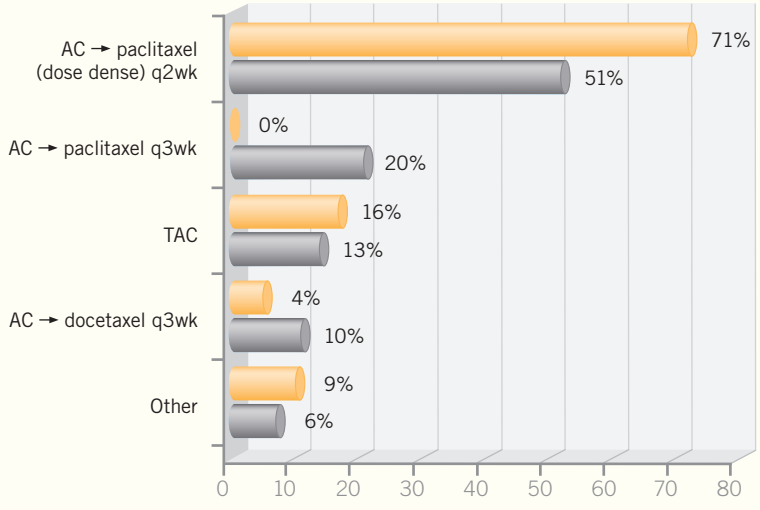


FIGURE 26

*In general, when using chemotherapy in the adjuvant setting in patients with **node-positive disease**, what tends to be the most common regimen you utilize?*



taining other agents (eg, docetaxel). It is intuitive that patients may be willing to endure the minor inconvenience of filgrastim administration to shorten duration of treatment and to gain therapeutically.

Meet The Professors 2006 (1)

DR MACKEY: I believe that TAC without growth factors is more toxic than dose-dense AC. We have data from a trial in which Miguel Martin, in Spain, treated node-negative patients with TAC or FAC. Early in the trial they thought, "Gee, for node-negative disease, TAC is quite tough," and they mandated G-CSF.

At that point, they found that the tolerability increased dramatically. It's not a randomized trial, and it's an intervention halfway through, but they found that not only did the febrile neutropenia rate drop, but the mucositis, fatigue and diarrhea decreased as well. In addition, the quality-of-life decrements that come with chemotherapy were less after G-CSF was initiated.

I agree that "naked" TAC without growth factors is probably tougher than dose-dense therapy with growth factors. However, I think that difference would be much less if you used primary prophylaxis with pegfilgrastim or filgrastim. I would suggest that if you were going to use it, use it with growth factor support.

Breast Cancer Update — Think Tank Issue 1, 2006

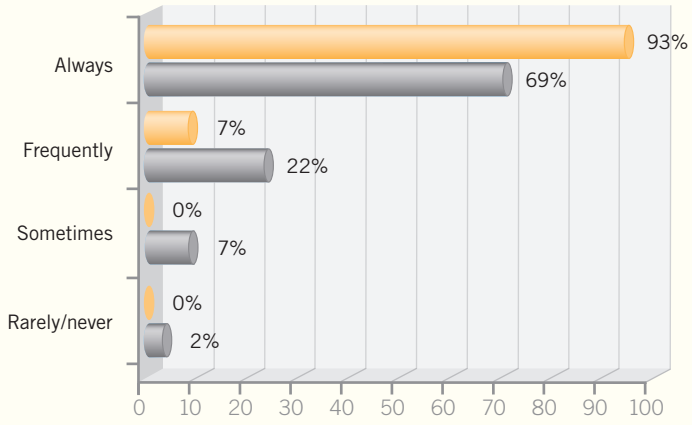
DR CHARLES L VOGEL: In our study, docetaxel was chosen as a representative regimen that could cause somewhere around a 20 percent risk of febrile neutropenia at 100 mg/m^2. All three endpoints — febrile neutropenia, febrile neutropenia-related hospitalization and use of anti-infectives — showed dramatic improvement with the addition of pegfilgrastim.

Most people would agree with the new NCCN guidelines stating that prophylactic growth factors should be used for patients with greater than 20 percent risk of febrile neutropenia. The use of prophylactic growth factors should also be considered in the intermediate-risk group (10 to 20 percent). Patients at low risk should not receive growth factors.

AC followed by docetaxel, AT and

FIGURE 27

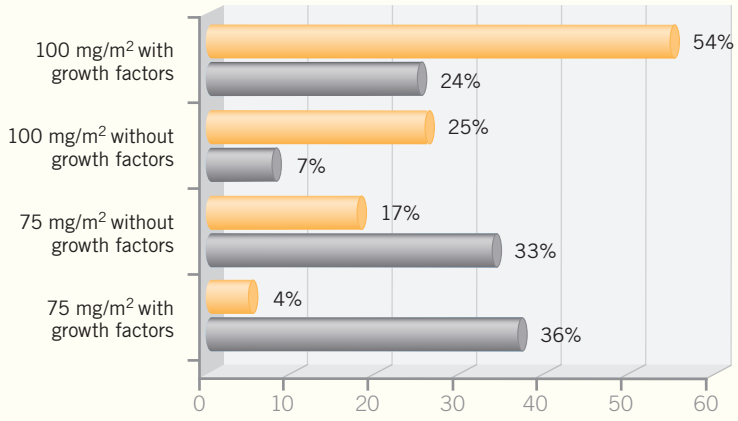
*When using TAC as adjuvant therapy, how often do you utilize myeloid growth factors preventively?**



* n = 31 investigators and 125 community oncologists who use TAC

FIGURE 28

*(Physicians using AC → docetaxel q3wk as adjuvant chemotherapy): What dose of docetaxel do you generally utilize?**



* n = 24 investigators and 111 community oncologists who use AC → docetaxel q3wk

TAC all have very high febrile neutropenia rates, and prophylactic growth factors should be strongly considered with these regimens. AC is considered an intermediate-risk regimen, as is docetaxel/capecitabine.

FAC, FEC and TC are regimens associated with borderline to low febrile neutropenia rates. Certainly, dose densification of any of these would be a reason to use prophylactic pegfilgrastim, as would the avoidance of dose reductions and delays. A third reason to consider it would be the factors that may cause patients to be at risk for febrile neutropenia.

Breast Cancer Update — Think Tank Issue 1, 2006

DR BURSTEIN: With regard to prophylactic growth factor support, I believe most of us would have a hard time consenting to a regimen associated with a one in five chance of a patient being hospitalized with febrile neutropenia compared to one that wasn't, simply for the administration of prophylaxis. So I don't find a problem with the recommendation for prophylactic treatment at 15 to 20 percent risk.

The problem is that we as a community haven't defined an acceptable level of febrile neutropenia. For instance, with nausea and vomiting, we all agree the desired goal is zero, so we liberally use prophylaxis.

For cancer pain, the goal is zero, so we liberally use pain medicine. We haven't said what we're willing to tolerate in the way of febrile neutropenia risk.

The only other anecdote I can offer is that as I administer AC every three weeks for patients destined to receive adjuvant trastuzumab, I'm struck by how many patients end up having dose delays and tweaks.

It's clearly more toxic than using dose-dense AC followed by paclitaxel with growth factor support.

This hasn't caused me to use G-CSF prophylactically in these settings, but it is impressive how predictable and clockwork-like every two-week AC with growth factor support is compared to other treatments.

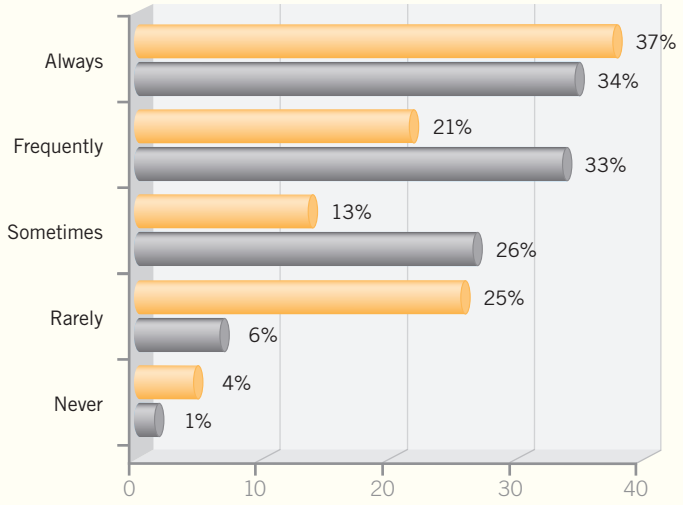
I believe if you asked patients whether they would take a growth factor for a four percent decrease in their chance of febrile neutropenia, they'd all say yes. Whether that is cost effective is a totally different question.

Breast Cancer Update 2006 (4)

DR STEPHEN E JONES: At the San Antonio Breast Cancer Symposium in 2005, we reported on a US Oncology adjuvant study in which we compared four cycles of standard-dose AC to four cycles of standard-dose TC (docetaxel and cyclophosphamide). Chemotherapy was administered before radiation

FIGURE 29

(Physicians using AC → docetaxel q3wk as adjuvant chemotherapy): How often do you utilize myeloid growth factors preventively ***with docetaxel****?**



* n = 24 investigators and 109 community oncologists who use AC → docetaxel q3wk

FIGURE 30

Are you aware of data presented by Dr Stephen Jones at the San Antonio Breast Cancer Symposium in December 2005 on the US Oncology trial of adjuvant TC (docetaxel/cyclophosphamide) versus AC?

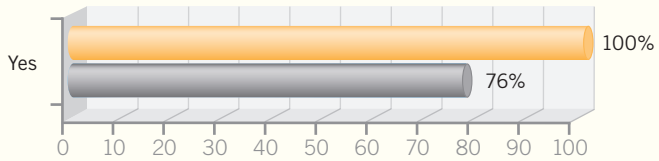
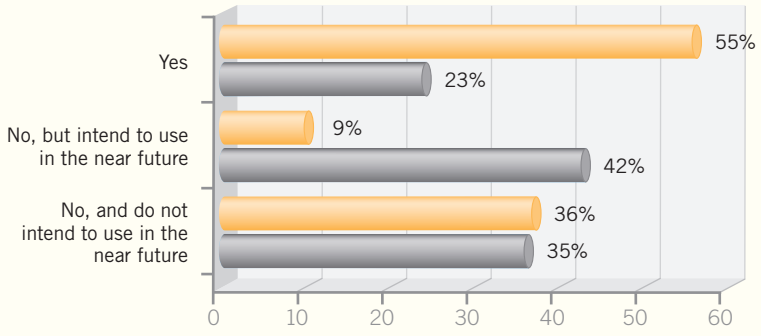


FIGURE 31

Have you utilized the adjuvant TC (docetaxel/cyclophosphamide) regimen?



therapy or tamoxifen, and we included patients with node-positive and higher-risk node-negative disease.

When we started this trial in 1997, everyone was interested in combining doxorubicin with the taxanes, but we felt that we didn't have enough data to combine docetaxel with doxorubicin. Consequently, we pursued this alternative route, which stands alone because it is one of the only nonanthracycline-containing regimens out there.

We now have mature results based on more than 170 events, with a median follow-up of 5.5 years. We have seen significantly fewer recurrences and events on the TC arm compared to the AC arm. I emphasized at San Antonio that the endpoint for this trial was disease-free survival, not overall survival. Overall survival was the secondary endpoint.

At five years, the disease-free survival was 86 percent for TC versus 80 percent for AC — a six percent absolute difference. The reduction in risk was roughly one third, and it was highly significant, with a *p*-value of 0.015. Also, a strong trend was favoring TC for overall survival — a three percent absolute difference at five years, with approximately a 24 percent reduction in the odds of dying from breast cancer.

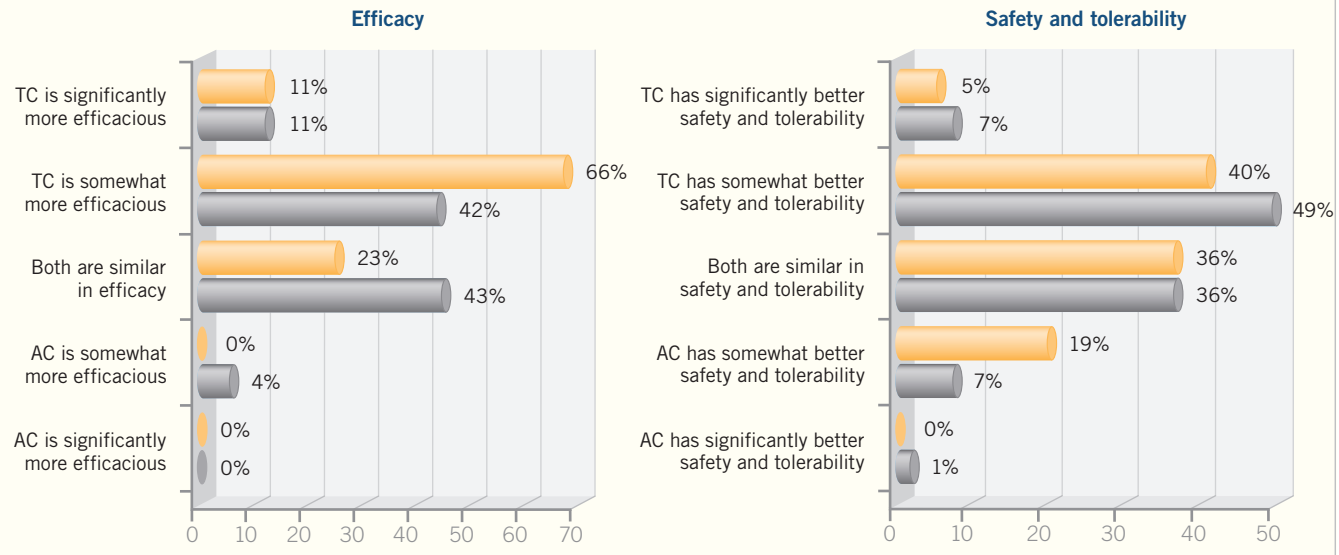
In general, TC was better tolerated. Some low-grade docetaxel-type side effects do occur, such as myalgias, arthralgias and edema, but they are fairly transient. The fever and neutropenia rates are also slightly higher; the numbers were 5.5 percent on the TC regimen and 2.5 percent on the AC regimen. We didn't use any prophylactic growth factors, but prophylactic antibiotics were used and encouraged.

The rate of congestive heart failure (CHF) with AC was probably lower than would be expected. The usual figure that's quoted is 0.5 to 1.0 percent; fortunately we haven't seen that kind of rate. We have no reason to believe that TC would cause cardiac toxicity.

AC brought significantly more Grade III/IV nausea and vomiting, despite antiemetics. That's an unpleasant side effect we didn't see with TC. I was

FIGURE 32

How would you compare TC (docetaxel/cyclophosphamide) to AC?



amazed at how much better tolerated TC was than AC.

Breast Cancer Update — Think Tank Issue 1, 2006

DR RAVDIN: In the data comparing docetaxel/cyclophosphamide to AC presented by Steve Jones at San Antonio in 2005, the hazard ratio for recurrence showed a 24 percent proportional advantage in survival for docetaxel/cyclophosphamide, which is as big a step as we usually take in our clinical trials, and it showed a 36 percent improvement in disease-free survival.

I believe the improvement in overall survival is real, and the correct interpretation isn't that it doesn't show a survival advantage but that it's underpowered to show a 24 percent advantage.

Breast Cancer Update 2006 (3): Miami Breast Cancer Conference Tumor Panel Discussion

DR O'SHAUGHNESSY: TC is definitely better tolerated than AC. What did not come out in the data set — but, if you took care of the patients on both arms, you saw it — was less fatigue with the TC because docetaxel at 75 mg/m^2 is not particularly fatiguing. With AC, you can get that kind of prolonged queasiness, and it "drugs you down" for a week or so in some patients. TC is much less nauseating and much better tolerated. It's really night and day. I have stopped using AC now in patients for whom I was using AC. Now I use TC because of the six percent absolute improvement in disease-free survival.

Breast Cancer Update 2006 (2)

DR SWAIN: ECOG-E1199, where the different schedules and different types of taxanes were compared, really showed that the weekly versus every three-week schedule didn't make any difference, and the drug, docetaxel or paclitaxel, didn't make any difference. So, in clinical practice, the best plan is to use whatever you're comfortable with.

For example, if you like AC followed by weekly paclitaxel, that is effective, or AC followed by docetaxel. I personally would use every three-week instead of weekly docetaxel. Basically, what ECOG-E1199 says is that we have a lot of different options.

Breast Cancer Update 2006 (3)

DR RAVDIN: The ECOG-E1199 trial asked two questions: Which taxane and which schedule are optimal as adjuvant therapy? Patients received AC, and then the standard arm was paclitaxel every three weeks for four cycles. Another arm was a substitution of docetaxel for paclitaxel, and two arms evaluated these agents in weekly regimens.

If you look at paclitaxel versus docetaxel, you see no superiority in a two-by-two comparison between the two agents. If you look at every three weeks versus weekly, you see no difference in efficacy.

However, the devil is in the details, and as clinicians we all want to know the one-by-four comparisons. The results are consistent with what we've seen in metastatic disease.

The weekly paclitaxel regimen was the best, with almost a 20 percent better hazard ratio than the standard arm. Docetaxel, given every three weeks, also looked somewhat better.

In both of those cases, however, the difference was a trend and was not statistically significant. The weekly paclitaxel arm looked best in terms of overall survival, but this is a very early analysis not dignified by *p*-values.

What about toxicity? The weekly paclitaxel arm seemed to provide additional benefit without additional risk

FIGURE 33

*Does the ER status of a tumor generally influence your decision **whether to recommend** adjuvant chemotherapy for **node-positive** tumors?*

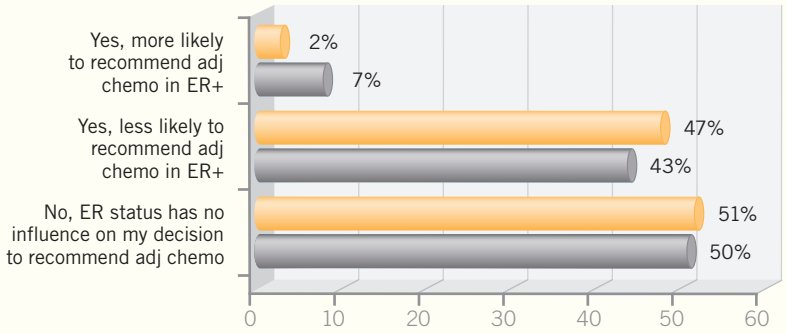
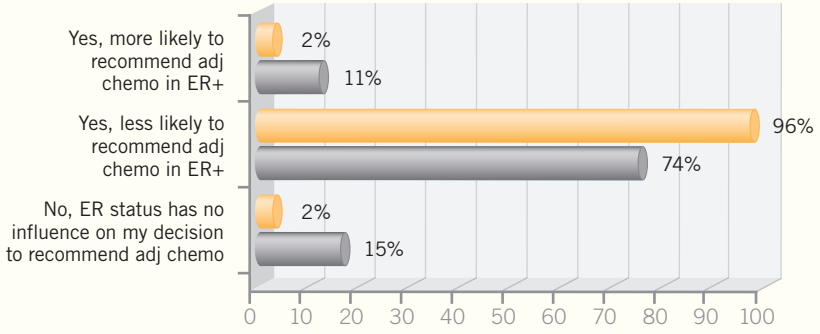


FIGURE 34

*Does the ER status of a tumor generally influence your decision **whether to recommend** adjuvant chemotherapy for **smaller node-negative** tumors?*



of febrile neutropenia, whereas the docetaxel arm was associated with additional febrile neutropenia.

A conclusion from this study has to be that weekly paclitaxel in adjuvant therapy appears promising, and the hazard ratios for the weekly arm of E1199 looked very similar to those of dose-dense therapy.

Breast Cancer Update — Think Tank Issue 1, 2006

DR HUDIS: Don Berry started the discussion of the impact of ER status on chemotherapy outcomes in the modern era by performing an unplanned retrospective analysis of CALGB trials on the basis of ER status.

He initially presented his three-study analysis at San Antonio in 2004 and compared the high-dose, every four-week CAF regimen to the standard AC arm of CALGB-9344. He then studied the AC paclitaxel arm of 9344 against the standard arm of the dose-dense 9741 trial.

For patients with ER-negative disease, the hazard for disease-free survival was significantly improved with each one of these steps — better CAF, addition of paclitaxel, dose-dense scheduling. Adding up the overall impact for ER-negative breast cancer, we see a profound chemotherapy effect.

In the subset of patients with ER-positive disease, the difference in each one of these steps was not statistically significant, but they were always favorable.

The point estimate for benefit is half the size for the patients with ER-positive disease compared to those with ER-negative disease. It is likely that it is still favorable, although the confidence interval does not exclude the possibility of no benefit at all.

To some degree, this has been wildly overinterpreted as suggesting that chemotherapy doesn't work in patients with ER-positive disease. It simply doesn't say that. It says that the magnitude of the benefit is likely to be much smaller than for those with ER-poor disease.

The important point is that when people say that the addition of dose-dense scheduling in 9741 doesn't yield much among patients with ER-positive disease, they're really not comparing apples to apples when they then look at the TAC-FAC data.

The TAC-FAC trial demonstrated hazard rates for risk reductions, which looked about the same in the ER-positives and the ER-negatives. The FAC control arm, of course, includes no paclitaxel or docetaxel.

You can't say that each individual step is or is not significant vis-à-vis another separate randomized trial. You can't compare these regimens head to head.

If you were to argue that you know to utilize TAC instead of dose-dense AC paclitaxel in a patient with ER-positive, node-positive disease, then you're presuming to know the results of NSABP-B-38.

I would argue that there is equipoise on this question and that either regimen is entirely appropriate for patients with ER-positive disease.

Breast Cancer Update — Think Tank Issue 1, 2006

DR WINER: I believe the bottom line is that if you take all patients with ER-positive breast cancer, the benefits of chemotherapy are dramatically less than in patients with ER-negative disease.

Almost certainly, some groups of women with ER-positive breast cancer derive no benefit, and others probably derive every bit as much benefit as the ER-negative group. It's not going to be chemo-

FIGURE 35

How would you compare the antitumor efficacy of TAC to dose-dense (DD) AC → paclitaxel?

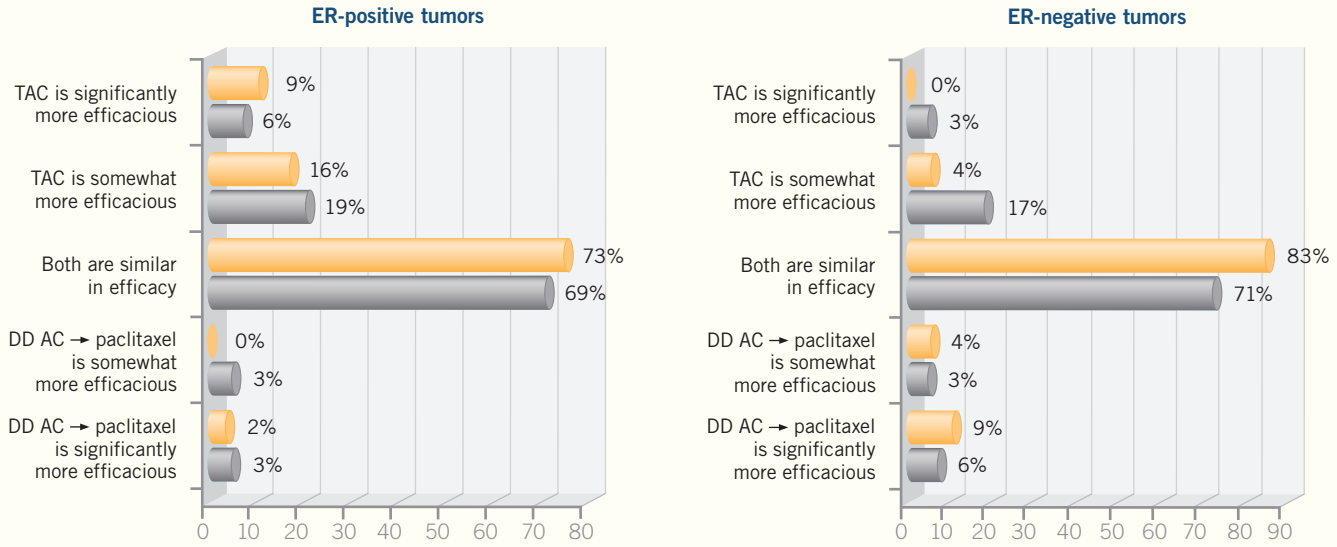
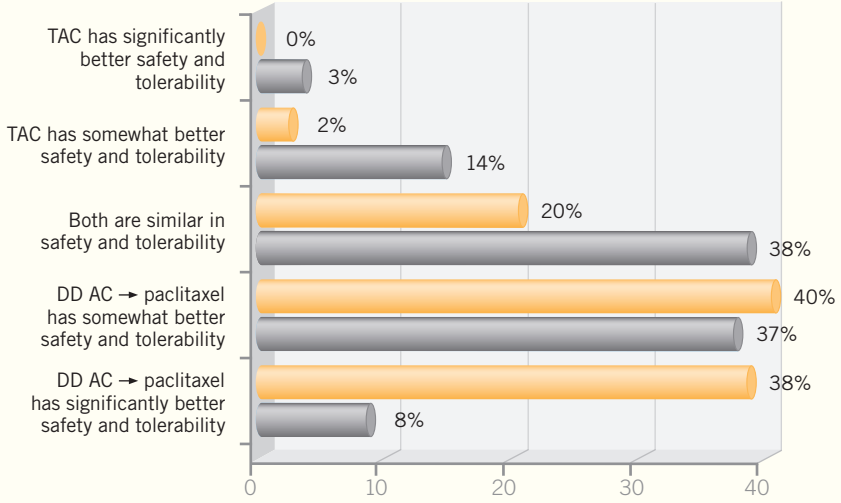


FIGURE 36

How would you compare the safety and tolerability of TAC to dose-dense (DD) AC → paclitaxel?



therapy agent specific, particularly when we get down to the level of taxanes.

Breast Cancer Update — Think Tank Issue 1, 2006

DR OSBORNE: The influence of ER status on the effects of chemotherapy is such an important question because 60 percent of all patients have ER-positive, PR-positive disease. Will anyone conduct a randomized trial of chemotherapy versus no chemotherapy or endocrine therapy alone versus the addition of chemotherapy in that subgroup?

Meet The Professors 2006 (1)

DR HUDIS: Without question, the Oxford Overview and virtually every study across the board ever done, including the TAC/FAC trial, show clear evidence of a greater magnitude of benefit for patients with ER-negative disease who receive chemotherapy than those in the ER-positive subset.

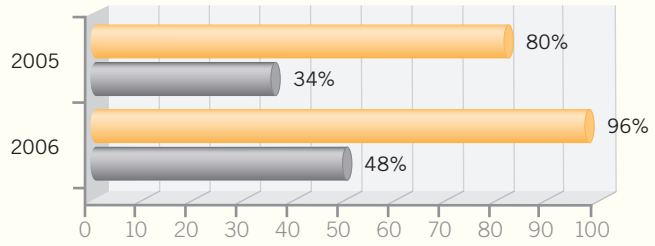
In the TAC to FAC comparison, the benefit in the ER-positive subset is statistically significant. In some of the other trials, it is not. That trial had the advantage of centralized ER testing and control over the hormone therapy.

When we conducted our studies in the CALGB, we recommended but didn't stipulate hormone therapy. We didn't do centralized ER testing. So our results are hypothesis generating. Our hypothesis is that chemotherapy is, on average, less effective in ER-positive than in ER-negative breast cancer. I don't think that's a big stretch.

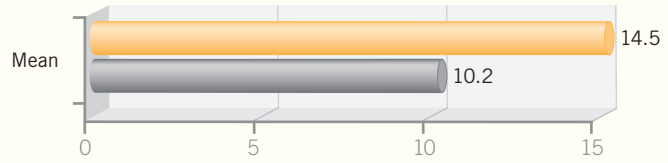
Whatever small benefit chemotherapy may offer patients with ER-positive disease is likely to play out over many, many years, and you need to have a long life expectancy to see that difference.

FIGURE 37

Have you ordered the Oncotype DX assay? (Percent answering yes)



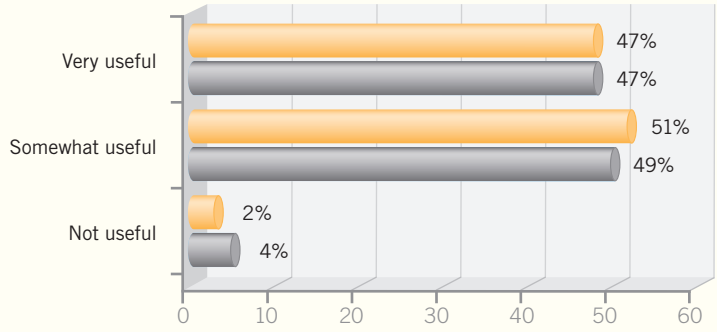
*If yes, for how many patients?**



* n = 43 investigators and 72 community oncologists who order Oncotype DX assay

FIGURE 38

*How useful is the Oncotype DX assay in **HER2-negative**, ER-positive tumors with negative nodes?**



* n = 43 investigators and 72 community oncologists who have ordered Oncotype DX assay

ER-positive breast cancer has a long, chronic relapse track. Not many people appreciate this, but by 30 years after diagnosis, it doesn't matter whether you had ER-positive or ER-negative disease, untreated. The overall risk of relapse and the overall survival is the same. So the notion that ER-positive disease is overall a better disease is undermined.

What's different is the timing of the recurrences. With ER-positive disease, you see the impact of therapy over the long haul. With ER-negative disease, you see it right up front.

For a young patient with a long life expectancy, I wouldn't be so quick to forgo that potential benefit. But the older you get, the longer you have to live to see the potential benefit and the more likely you are not to get there.

Breast Cancer Update 2005 (3)

DR SOONMYUNG PAIK: NSABP-B-20 included women with node-negative, ER-positive disease. It was a three-arm design, and patients were randomly assigned to tamoxifen alone or tamoxifen concurrent with either CMF or methotrexate followed by 5-FU.

Our study of the Oncotype DX assay was a retrospective analysis of that completed trial.

We only had tissue blocks available for approximately 30 percent of the entire study cohort, so it's a subset; however, the subset and the entire cohort were comparable.

We repeated the Oncotype DX assay on the tamoxifen arm to ensure the assay was reproducible, and we demonstrated that it is reproducible, which is encouraging.

It is important to note that we evaluated the NSABP-B-20 chemotherapy arms to address whether the assay predicted chemotherapy responsiveness.

We went into that study with an a priori hypothesis, based on the data presented at the 2004 ASCO meeting by Dr Luca Gianni's group in Milan evaluating samples from a neoadjuvant trial they performed with paclitaxel and doxorubicin.

They demonstrated a correlation between the Genomic Health recurrence score and pCR rate.

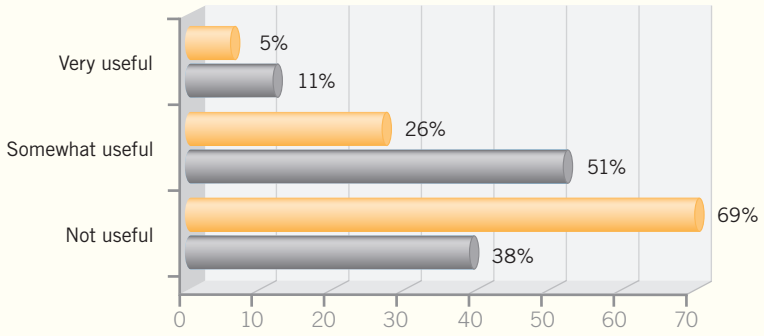
The higher recurrence rate correlated strongly with the higher pCR rate. The overall pCR rate was approximately 25 percent in the patients with high-risk disease, and there was no pCR in patients with low-risk disease.

We hypothesized that the benefit from chemotherapy in NSABP-B-20 would be almost negligible in patients with low-risk disease and high in patients with high-risk disease. The results of this study are striking and unlike anything I've ever seen.

The absolute benefit from chemotherapy is negative in the low-risk group and zero in the intermediate-risk group. In the high-risk group, the absolute

FIGURE 39

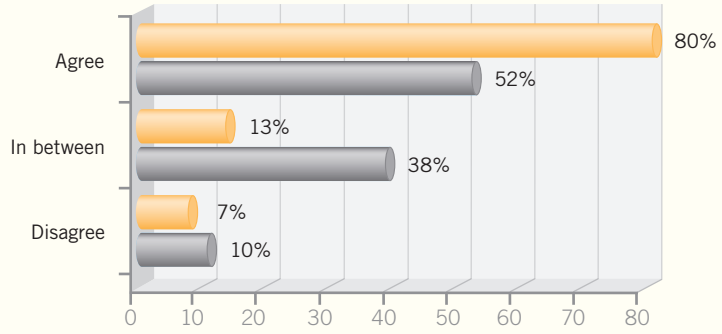
*How useful is the Oncotype DX assay in **HER2-positive**, ER-positive tumors with negative nodes?**



* n = 43 investigators and 72 community oncologists who have ordered the Oncotype DX assay

FIGURE 40

For patients with ER-positive, HER2-negative, node-negative tumors, the Oncotype DX assay should be offered when both the doctor and patient are "on the fence" about whether to use adjuvant chemotherapy.



improvement in distant recurrence at 10 years is 28 percent, or a relative risk reduction of 75 percent.

The data in the low-risk group are, in a sense, not relevant because the baseline risk after tamoxifen is so low — 6.8 percent — that it's a moot point whether they need chemotherapy.

In the intermediate-risk group the confidence interval overlaps with one, so whether patients with intermediate-risk disease gain any benefit remains a question.

Breast Cancer Update — Think Tank Issue 1, 2006

DR DANIEL F HAYES: The patients with node-negative, ER-positive disease in the TAILORx, or ECOG-PACCT-1, study will all be profiled by the Oncotype DX assay. Those patients with a good recurrence score of 11 or lower will receive hormone therapy only.

Those with a high recurrence score of 25 and higher will all receive hormone therapy and chemotherapy of "dealer's choice."

Those in the intermediate group will be randomly assigned to receive chemotherapy or not (investigator's choice). They then will all receive hormone therapy, also at the investigator's choice.

Meet The Professors SABCS 2004

DR HYMAN MUSS: One of the exciting trials we have ongoing in North America is CALGB-49907. This is a trial that essentially compares standard chemotherapy — four cycles of AC or CMF with oral cyclophosphamide — to six cycles of capecitabine for elderly patients. Physicians can select the standard chemotherapy for patients randomly assigned to that arm.

We're excited about the trial and like to believe it's an equivalence study, as some background data suggest that oral capecitabine is as good as standard therapy. It would be nice if we had an oral regimen because I think people would rather be at home than in our clinics all the time.

CALGB-49907 Protocol. calgb.org

A recent randomized phase II trial, comparing single-agent capecitabine and CMF as first-line therapy in patients with metastatic breast cancer who were 55 years and older (median age 69 years), demonstrated the response rate to capecitabine alone (25 percent) at a dose of 2510 mg/m^2 per day for 14 days, every three weeks was superior to intravenous CMF (16 percent).

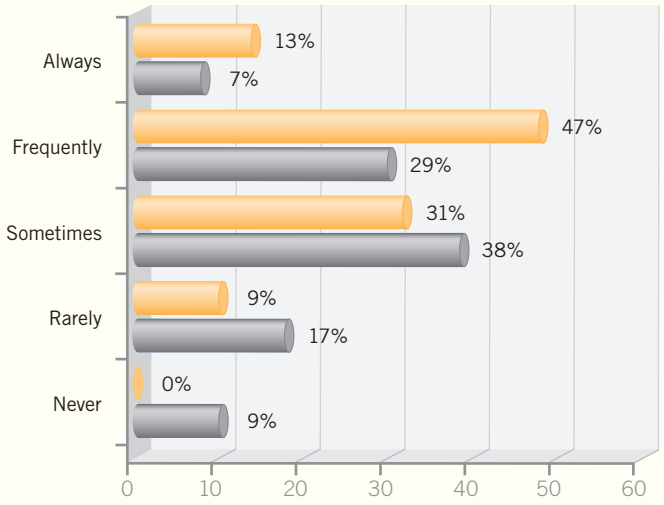
Grade 3 or 4 hand-foot syndrome was seen in 16 percent of patients on capecitabine and none on CMF, Grade 3 or 4 diarrhea in 8 percent with capecitabine and 3 percent with CMF, and Grade 3 or 4 hematological toxicity in 20 percent with capecitabine and 47 percent with CMF.

In another Phase II randomized trial comparing capecitabine in the same dose and schedule as above with paclitaxel 175 mg/m^2 every three weeks, the response rate was 36 percent for 22 patients on capecitabine and 21 percent for 22 patients on paclitaxel.

These data suggest that the efficacy of capecitabine in patients with metastatic disease is similar to CMF or paclitaxel.

FIGURE 41

If CALGB-49907 demonstrates equal efficacy of capecitabine to AC or CMF in the adjuvant setting in elderly women, how often would you utilize adjuvant capecitabine off protocol rather than AC or CMF in elderly women?



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Paik S. **Molecular profiling of breast cancer.** *Curr Opin Obstet Gynecol* 2006;18(1):59-63. **Abstract**

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26. **Abstract**

Roche H et al. **Five years analysis of the PACS 01 trial: 6 cycles of FEC100 vs 3 cycles of FEC100 followed by 3 cycles of docetaxel (D) for the adjuvant treatment of node positive breast cancer.** San Antonio Breast Cancer Symposium 2004;**Abstract 27**.

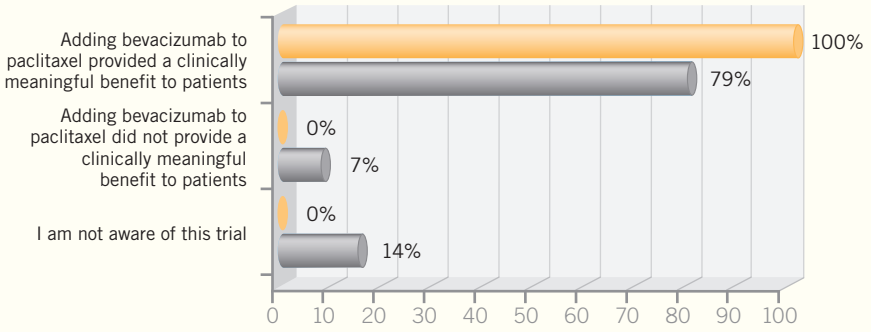
Sparano JA et al. **Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: Results of North American Breast Cancer Intergroup Trial E1199.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 48**.

Venturini M et al. **Dose-dense adjuvant chemotherapy in early breast cancer patients: Results from a randomized trial.** *J Natl Cancer Inst* 2005;97(23):1724-33. **Abstract**

Vogel CL et al. **First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study.** *J Clin Oncol* 2005;23(6):1178-84. **Abstract**

FIGURE 42

What is your impression of the ECOG-E2100 study evaluating bevacizumab with paclitaxel as first-line therapy for metastatic disease?



Miami Breast Cancer Conference Tumor Panel Discussion

DR BURSTEIN: The exciting thing about ECOG-E2100 was it really established a principle that anti-angiogenic therapy can be effective in advanced breast cancer. We had the results from the previous trial of anthracycline- and taxane-treated patients who were randomly assigned to capecitabine with or without bevacizumab, and in that study it was hard to see much significant clinical benefit.

It was always hard to square that result with the data that were seen in colorectal cancer. It's not clear that one is such a vascular-driven tumor and the other would not be. So, from a conceptual point of view, the ECOG-E2100 really opens up a whole new area for us to try and exploit to help take better care of cancer patients, and that's why I think it's a very compelling study. It really gives us something tremendous to build upon.

Meet The Professors 2005 (3)

DR O'SHAUGNESSY: It's not too surprising that E2100 was a positive trial because as a single agent, it has activity. It also had activity in the capecitabine randomized Phase III trial. That was a late-line population, and it's difficult to change the median of anything when only a small percentage of patients benefited.

I guess the number one thing I want to see are some interesting exploratory subset analyses. For example, is the benefit of bevacizumab going to be largely seen in the higher-grade tumors, such as ER-negative, PR-negative or perhaps HER2-positive tumors?

What about indolent disease? You might have patients with some indolent biology, so I need to see the data. However, this sounds like a real advance for select patients for whom you believe it will be safe to administer bevacizumab.

Breast Cancer Update 2006 (4)

DR KATHY D MILLER: In the design of ECOG-E2100, we allowed patients who had received a taxane-containing adjuvant regimen to enroll as long as their disease-free interval was at least 12 months. We did that for pragmatic reasons because the taxanes were being used more frequently in the adjuvant setting. We thought it would be reasonable to consider re-treating those patients if their disease-free interval was at least a year.

Approximately 18 percent of our patients had received a taxane-containing regimen. Their hazard ratio was 0.38, which was the best hazard ratio of all of the clinically based subsets. For those patients, that translated into an improvement not from six to 11 months but from four to just more than 12 months in median progression-free survival.

We talked about whether we should have a crossover in ECOG-E2100, and we decided not to for a couple of practical reasons. One was that it would have made the trial a lot more complicated and expensive. Also, our primary endpoint was progression-free survival, so having a crossover would not have contributed to our primary endpoint.

Breast Cancer Update 2005 (7)

DR WINER: I believe the results of ECOG-E2100 are impressive enough that, in the absence of a contraindication to bevacizumab, I would now use it in a first-line setting, optimally in combination with paclitaxel as administered in the study.

I doubt that the interaction is specific between paclitaxel and bevacizumab, although I'm well aware that when given with capecitabine in more advanced disease, bevacizumab seemed to be less active. I believe that's probably related to the setting rather than the drug.

Breast Cancer Update 2005 (6)

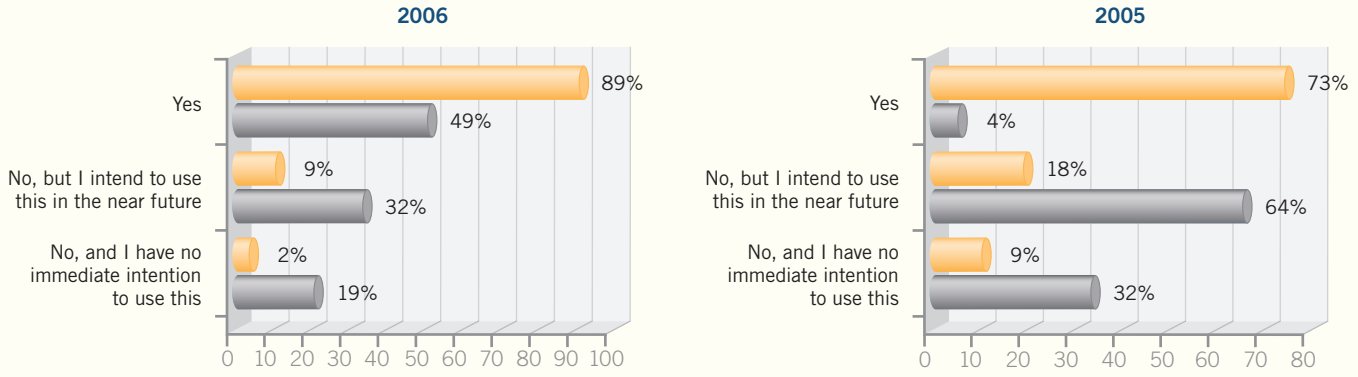
DR SLEDGE: As a result of the previous toxicity seen in the lung cancer trial, we had very stringent criteria for discontinuing E2100 if we saw an excess number of patients developing Grade IV hypertension or bleeding. When the trial was initiated, the National Cancer Institute had significant concerns about patient safety as a result of the initial experience with bevacizumab in lung cancer.

Fortunately, early analyses demonstrated that was not an issue in breast cancer. The side effects were relatively minimal. Predominantly, we saw mild to moderate increases in blood pressure, which is readily handled from a clinical standpoint. Of course, we'll have to be careful with the hypertension as we move bevacizumab into the adjuvant setting. We also saw a low incidence of seri-

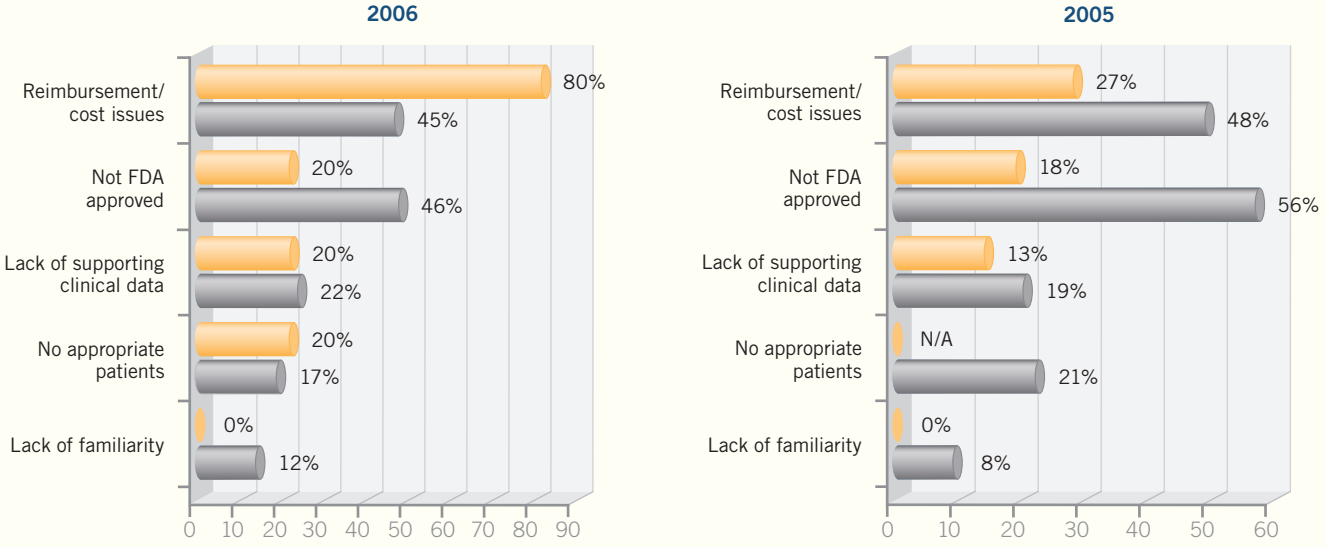
CLINICAL INVESTIGATORS COMMUNITY ONCOLOGISTS

FIGURE 43

Have you used bevacizumab for breast cancer patients in the metastatic setting?



Which of the following best explains the reasons you have not yet used bevacizumab? (May have more than one response)*



2006 * n = 5 clinical investigators and 76 community oncologists who have not used bevacizumab

2005 * n = 12 clinical investigators and 96 community oncologists who have not used bevacizumab

ous bleeding. Overall, bevacizumab was a nontoxic addition to chemotherapy.

Breast Cancer Update 2006 (4)

DR MILLER: Adding bevacizumab increases the risk of arterial thrombotic events, although to a very modest degree. We know a little about the risk factors in that the risk seems to be preferentially borne out in patients who are older than age 65 or those who have had previous arterial thrombotic events, particularly MI, TIA or stroke.

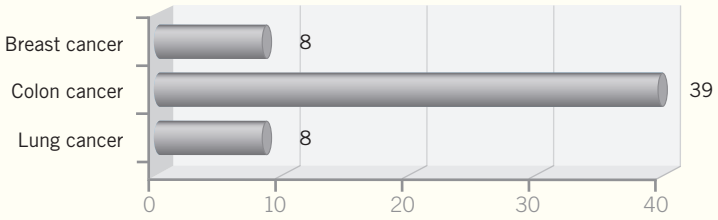
No reports associate cardiomyopathy or congestive heart failure with bevacizumab in any of the trials that either did not use concurrent anthracyclines or were in patient populations who would not have been previously treated with anthracyclines. So this is an issue specific to patients with breast cancer, sarcoma or leukemia, for which anthracyclines are used.

In the randomized bevacizumab/capecitabine trial, two patients had congestive heart failure or cardiomyopathy in the capecitabine-alone group compared to seven in the capecitabine with bevacizumab group. That sounds like an increase, but the overall event rate was so low that, statistically, those numbers were not different.

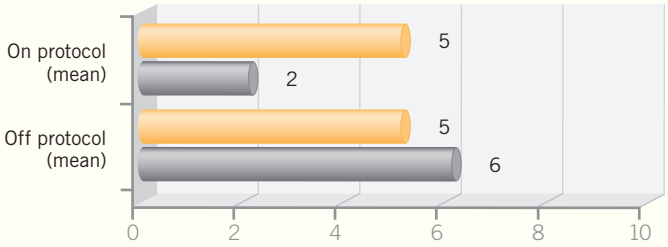
In ECOG-E2100, we didn't see any sign of congestive heart failure when comparing the two groups. In Sandy Swain's 21-patient experience, which is

FIGURE 44

In how many patients with the following tumor types have you used bevacizumab? (Mean)



*For the breast cancer patients with whom you used bevacizumab: How many received it?**



* n = 40 clinical investigators and 74 community oncologists who have used bevacizumab

the only breast cancer trial that has used an anthracycline and bevacizumab concurrently, none of the patients had clinical congestive heart failure, but two of them showed a decrease in their ejection fraction to less than 40 percent.

Breast Cancer Update — Think Tank Issue 1, 2006

DR WINER: Three issues have led people to be less enthusiastic about bevacizumab use in first-line metastatic breast cancer. One is that the E2100 data apply to a large subset of patients. They would be happier if it were targeted to a smaller specific subset of patients. The second is that they are less enthusiastic and unsure of what to do with the capecitabine trial. And the third and very real issue is the cost.

Breast Cancer Update — Think Tank Issue 1, 2006

DR SLEDGE: From a quality-of-life standpoint, those of us who have used bevacizumab have found it an incredibly easy drug for patients. The toxicity is truly trivial compared to every single chemotherapeutic agent in the therapeutic armamentarium. So it's not had any major negative effect on any significant percentage of patients in terms of quality of life and increase in toxicity.

However, these are the issues regarding bevacizumab extension: First, safety of prolonged exposure to bevacizumab; second, response to second-line combination therapy with bevacizumab; third, issues surrounding resistance to antiangiogenic therapy; and then, finally, the cost of therapy.

Breast Cancer Update 2006 (4)

DR MILLER: One of the trials that we activated shortly after we had the results from ECOG-E2100 was a Phase II trial known as XCaliBr, which uses the capecitabine/bevacizumab combination from the earlier Phase III trial but as first-line therapy for patients with metastatic disease. It's essentially the ECOG-E2100 patient population using the regimen from the capecitabine/bevacizumab trial. We thought that was a reasonable trial because we had ample safety data with the combination, and we knew that adding bevacizumab to capecitabine improved the response rates.

It potentially will provide patients in that first-line chemotherapy setting another option and one that would be oral and wouldn't cause alopecia, if we see similar response rates and progression-free survival in a decent-sized Phase II study.

Our trial with refractory patients found a doubling of response rates. We have data that strongly suggest this would be active. What we don't know is whether we'll have the same response rate and progression-free survival as with the paclitaxel-based regimen. I believe that would be an important piece of data clinically to allow people greater flexibility in their first-line regimen of chemotherapy with bevacizumab.

Breast Cancer Update 2006 (3)

DR GRADISHAR: I still believe that capecitabine is a good up-front agent to use in metastatic disease for many patients, and that hasn't changed with the bevacizumab data. However, the data that emerge from the XCaliBr study may provide justification for using capecitabine with bevacizumab, assuming the data are positive and comparable to what we saw in the E2100 study.

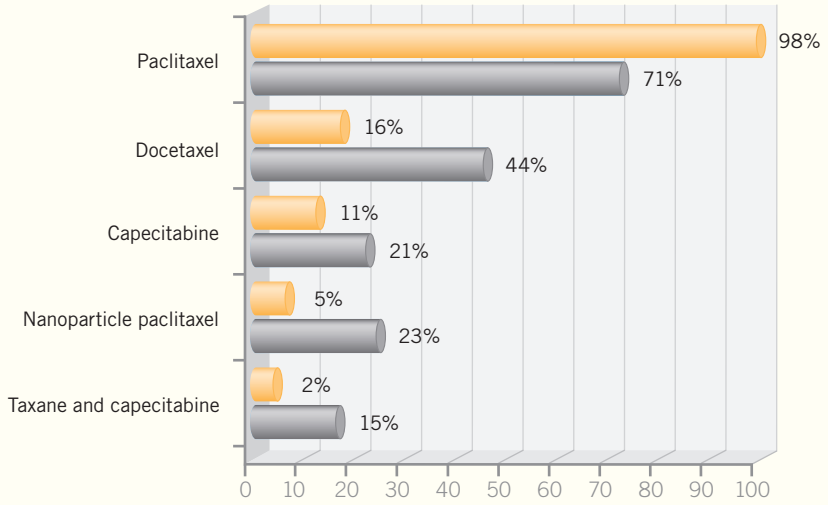
Capecitabine is comparable to our most active chemotherapy drugs, but I don't view any drug as the best agent in a particular situation. I would use capecitabine for patients with minimal visceral disease such as small liver metastases, but docetaxel or nanoparticle albumin-bound (*nab*) paclitaxel would be fine as well. It's a judgment call that you make with each patient depending on her preferences.

Miller KD et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005;23(4):792-9.

The addition of bevacizumab to capecitabine clearly increased response

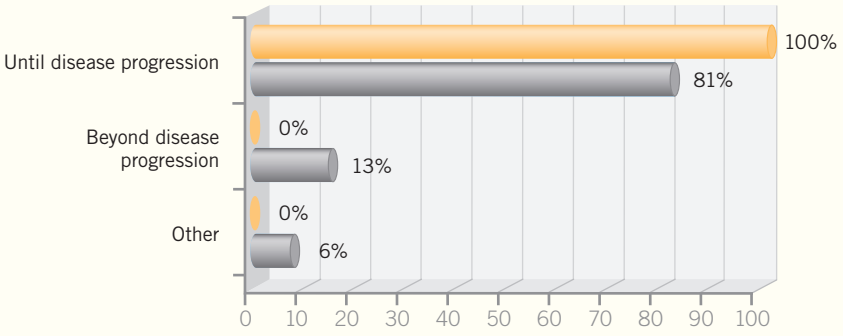
FIGURE 45

If you have used or plan to use bevacizumab in metastatic breast cancer, which agents would you combine with it? (May have more than one response)*



* n = 44 clinical investigators and 122 community oncologists who use or plan to use bevacizumab

*If you have used or plan to use bevacizumab, for how long would you use it?**



* n = 45 clinical investigators and 135 community oncologists who use or plan to use bevacizumab

rates, whether assessed by the IRF or the investigators, without significantly adding to the overall toxicity of the treatment regimen.

Despite improvement in ORR, the duration of the responses was short with respect to PFS, and the proportion of long-term responders was similar in the two groups.

Burstein HJ et al. Metronomic chemotherapy with and without bevacizumab for advanced breast cancer: A randomized phase II study. San Antonio Breast Cancer Symposium 2005;Abstract 4.

Metronomic chemotherapy administered to this patient population using low dose oral cyclophosphamide and methotrexate had minimal clinical activity by itself. In combination with metronomic chemotherapy and bevacizumab, there was a higher clinical activity rate noted in women with advanced breast cancer.

We believe the combination therapy is reasonably well tolerated and lacks many of the acute side effects of chemotherapy.

We are in the process of performing correlative studies of VEGF levels and circulating endothelial cells to both understand the mechanism of action of these treatments and to try and identify patients who might selectively benefit, and we believe that further investigation of this treatment option is warranted.

To that end, we have activated a study at Dana-Farber, Indiana University, and UCSF, in which patients who have residual invasive breast cancer after receiving neoadjuvant chemotherapy will be assigned to treatment cohorts where they will receive one year of bevacizumab or one year of bevacizumab with six months of metronomic chemotherapy in a group of women who by some of the definition have resistance to traditional chemotherapy.

Breast Cancer Update 2005 (8)

DR VICENTE VALERO: There are two combination regimens that have proved to be superior to single-agent taxane therapy for metastatic disease. One is gemcitabine with paclitaxel, which was compared to paclitaxel alone. The data were presented at ASCO, showing an improvement in time to progression and preliminary evidence of an increase in overall survival.

The other study compared docetaxel with capecitabine to docetaxel alone and also showed a time to progression and overall survival advantage.

Based on the evidence, both of these combinations are reasonable for first-line chemotherapy of metastatic disease. However, in some patients, sequential chemotherapy is our preference.

I tend to use more sequential single-agent chemotherapy, but I believe the role of combination chemotherapy in some instances is well documented by the two studies I just mentioned.

FIGURE 46

The cost of bevacizumab is so high that it should not be prescribed in the metastatic breast cancer setting even if reimbursement were not an issue.

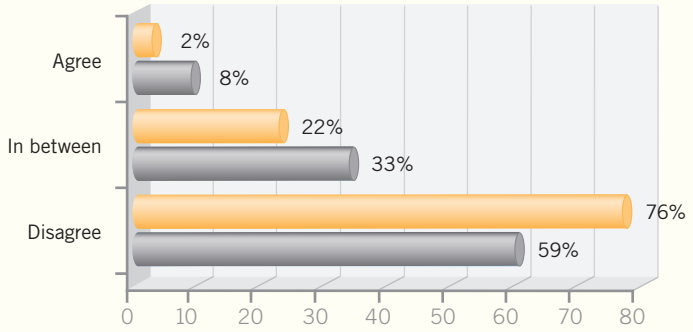
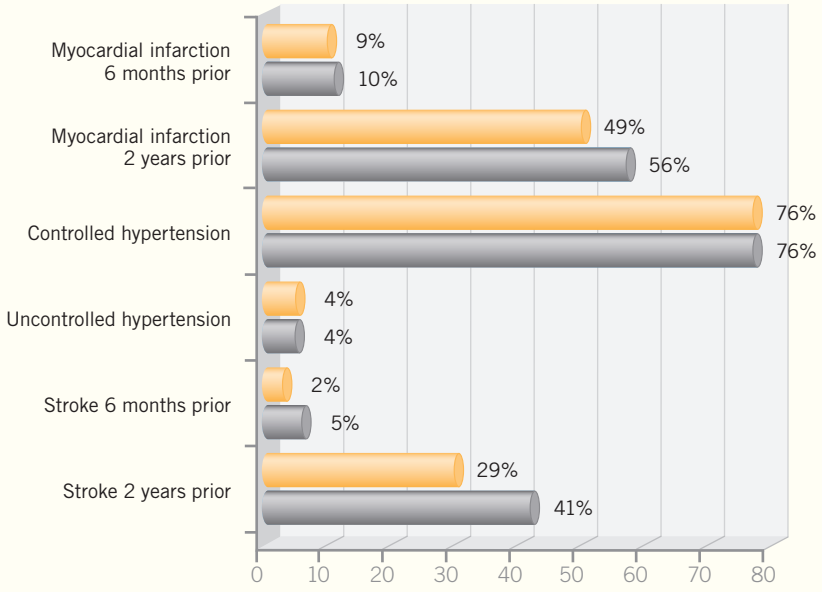


FIGURE 47

If reimbursement and cost were not an issue, would you recommend bevacizumab for a 65-year-old woman who received prior AC and presents with asymptomatic metastatic breast cancer with: (Percent answering yes)



For women who have symptomatic breast cancer with visceral involvement, it is essential to have a response to alleviate the symptoms and improve their quality of life. For those patients, despite the enhancement of the adverse events, I strongly consider combination chemotherapy.

Eniu A et al. Weekly administration of docetaxel and paclitaxel in metastatic or advanced breast cancer. Oncologist 2005;10(9):665-85.

Optimizing the dose and schedule of taxane therapy to maximize antitumor activity while maintaining a favorable toxicity profile remains an important goal in MBC. Weekly, rather than the standard every-3-weeks, dosing of docetaxel and paclitaxel at lower doses is one way to provide an efficacious method of drug delivery while maintaining a favorable toxicity profile.

Various studies support weekly taxane dosing as an active regimen in MBC, even in heavily pretreated, refractory disease and in elderly patients or those with poor performance status. Importantly, this regimen is associated with a low incidence of severe hematologic toxicities and acute nonhematologic toxicities.

Jones SE et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 2005;23(24):5542-51.

This is the first clinical trial to compare directly the taxanes, docetaxel and paclitaxel, as monotherapy for patients with advanced breast cancer. Using US Food and Drug Administration-approved doses and schedules for each agent, this phase III study has demonstrated that docetaxel is superior to paclitaxel in TTP (5.7 v 3.6 months; P <.0001), response duration (7.5 v 4.6 months; P <.01), and OS (15.4 v 12.7 months; P <.03).

The overall response rate was also greater with docetaxel (32% v 25%; P < .10). The survival advantage for docetaxel was observed despite the increased incidence of toxicities leading to dose reductions and treatment withdrawal, and the slightly greater use of salvage treatment in patients randomly assigned to paclitaxel.

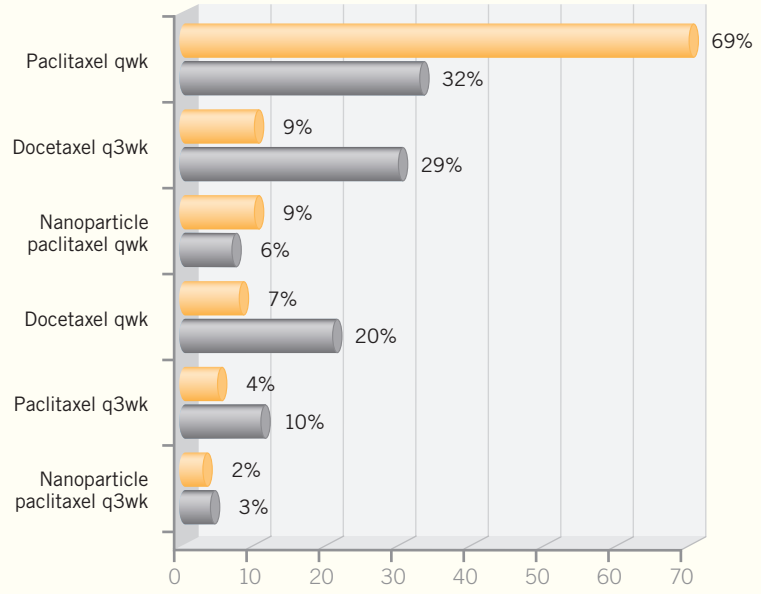
The results of this study are consistent with those reported for previous phase III studies of single-agent docetaxel and paclitaxel.

Ghersi D et al. A systematic review of taxane-containing regimens for metastatic breast cancer. Br J Cancer 2005;93(3):293-301.

We compared the results of randomized trials comparing taxane-containing chemotherapy regimens with regimens not containing a taxane in women with metastatic breast cancer. The specialized register of the Cochrane Breast Cancer Group was searched in March 2004. Eligibility was assessed and data extract-

FIGURE 48

For a patient who has received adjuvant AC and has disease recurrence, in whom you want to utilize a single-agent taxane, which of the following best describes which agent and schedule you would most likely use?



ed from eligible studies by two reviewers. Hazard ratios (HR) were derived for time-to-event outcomes, and a fixed-effect model was used for meta-analysis. Tumor response rates were analyzed as dichotomous variables.

Of 21 eligible trials, 16 had published some results and 12 data on overall survival. An estimated 2621 deaths among 3643 women suggest a significant difference in overall survival in favor of taxane-containing regimens (HR 0.93, 95% confidence interval (CI) 0.86-1.00, P=0.05). The treatment effect on survival was similar if only trials of first-line chemotherapy were included, although not statistically significant.

There appeared to be an advantage for taxanes in time to progression (HR 0.92, 95% CI 0.85-0.99, P=0.02) and overall response (odds ratio (OR) 1.34, 95% CI 1.18-1.52, P<0.001). There was significant heterogeneity across the trials (P<0.001), partly because of the varying efficacy of the comparator regimens. Taxane-containing regimens improved overall survival in women with metastatic breast cancer. Taxane-containing regimens are more effective than some, but not all, nontaxane-containing regimens.

Breast Cancer Update 2006 (3)

DR GRADISHAR: In terms of first-line taxanes in the metastatic setting, the data are still more abundant with both paclitaxel and docetaxel than with *nab* paclitaxel, so if basing a decision on the length of experience, those agents have been around for a longer time.

However, I see no reason to believe that *nab* paclitaxel will prove inferior to those drugs with more data. I believe *nab* paclitaxel will compare favorably, if not prove to be superior.

When you examine clinical trials that have evaluated docetaxel or paclitaxel in similar patient populations with metastatic disease, the indirect evidence shows the activity of *nab* paclitaxel to be comparable to docetaxel. These agents may have similar antitumor effects, so one should consider other factors, including toxicities, patient convenience and cost.

If *nab* paclitaxel can offer the same antitumor effect as docetaxel and paclitaxel along with advantages in terms of lack of premedication and shorter infusion time, whether or not it would become the preferred agent is an important question. When you think of busy office practices, the throughput of patients and convenience to patients are important. An upside to *nab* paclitaxel clearly is the shorter infusion time and the lack of need for premedication.

As for the higher acquisition cost of *nab* paclitaxel, economic analyses suggest that some of the downstream expenses related to administering paclitaxel or docetaxel — specifically the costs of premedications and antibiotics or growth factors to manage the neutropenias or cytopenias — result in a net savings with the use of *nab* paclitaxel.

Although we need more information, I believe we shouldn't necessarily be put off by the up-front cost; we should take into account the whole package of managing the patient's treatment.

Smith I. Goals of treatment for patients with metastatic breast cancer. Semin Oncol 2006;33(1 Suppl 2):2-5.

The key goal in the treatment of metastatic breast cancer is to prolong survival, with an emphasis on restricting treatment-related toxicity as much as possible. Despite the plethora of treatment modalities available in metastatic breast cancer, significant survival differences are relatively uncommon. Symptom relief and quality of life are other important, clinically validated measurement instruments.

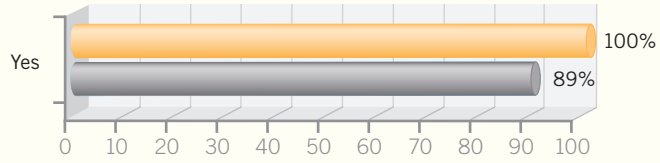
Symptom relief in particular is not used as widely used as it could be, in contrast to lung cancer where it has been proven clinically informative. Finally, time to disease progression is an increasingly used primary endpoint in comparing treatments for metastatic breast cancer; this measure includes both patients who achieve an objective response, and those whose disease may be stabilized with treatment.

Special Edition BCU: Proceedings from Two Medical Oncology Educational Forums, 2005

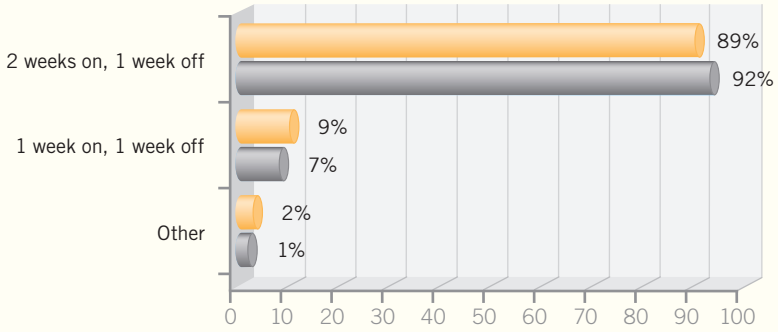
DR RAVDIN: Capecitabine has some

FIGURE 49

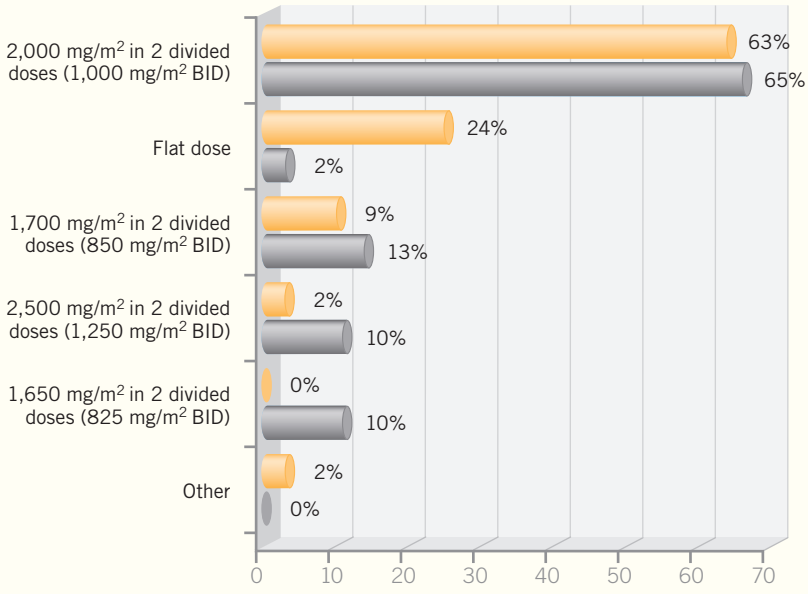
Do you use capecitabine for metastatic breast cancer in your practice?



*How do you generally schedule capecitabine in this setting?**



*How do you generally dose capecitabine monotherapy when using it in a 2 weeks on/1 week off schedule?**



* n = 45 clinical investigators and 134 community oncologists who use capecitabine

attractive features. In terms of toxicity and response, I view it as something that bridges the gap between hormonal therapy and intravenous chemotherapy. Particularly when dosed a bit lower than the package insert dose, it's tolerable for most patients, and they don't experience nausea, vomiting or hair loss, almost as if they were receiving an endocrine agent. It's an oral agent — we don't have to put in a line — so it's easier for patients to accept. I think all those features make it an attractive agent.

Actually, I'm surprised that it isn't more commonly used in the community because I think it's one of those agents that is generally tolerated with repeated use. With a lot of other agents, patients begin to get tired when you get in six cycles.

Breast Cancer Update 2005 (8)

DR VALERO: When using capecitabine in patients with a good performance status who are not heavily pretreated, I use 2,000 mg/m^2 daily in two divided doses for 14 of 21 days.

After two cycles of therapy, I will consider escalating the dose if the patient has no toxicity. For patients with a poor performance status, for whom I'm going to consider capecitabine as a second- or third-line therapy — patients who are fragile — I may use 1,750 mg/m^2 daily.

We recently published in the *Annals of Oncology* about our experience at MD Anderson with different doses of capecitabine. We believe that a lower dose is preferable, although the FDA-approved dose is 2,500 mg/m^2.

I believe this publication confirms what we do in the clinic. When you have a Phase II study in several locations, but you select people out and monitor them very closely, capecitabine can be administered at a higher dose.

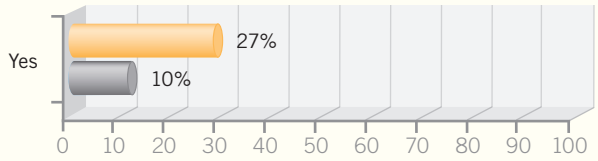
I could deliver capecitabine at 2,500 mg/m^2 daily, but it needs close monitoring with a patient who is able to follow closely with her oncologist.

In the clinical trials, as soon as the patients start to develop early signs of mucositis, diarrhea or hand-foot syndrome, capecitabine is stopped immediately.

Then the patient reports to the oncologist or the research nurse for instructions. Then you restart the capecitabine, and you may restart it at a lower dose. So it needs some close monitoring.

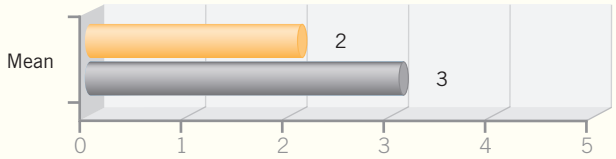
FIGURE 50

*Have you used capecitabine plus bevacizumab off protocol in the metastatic setting?**



* n = 45 clinical investigators and 134 community oncologists who use capecitabine

*If yes, with how many patients in the last year?**



* n = 12 clinical investigators and 13 community oncologists who use bevacizumab in combination with capecitabine

In general, most patients at the end of the day receive an average dose of around 2,000 mg/m^2 daily as a single agent. In some patients, I also use even lower doses — 1,500 mg/m^2 daily.

The bottom line is that the evidence that a lower dose is efficacious is just not there. Our study is one of the first that provides information, but it was not a prospective study to assess response and time to progression in a well-designed Phase II fashion.

Hennessy BT et al. Lower dose capecitabine has a more favorable therapeutic index in metastatic breast cancer: Retrospective analysis of patients treated at MD Anderson Cancer Center and a review of capecitabine toxicity in the literature. Ann Oncol 2005;16(8):1289-96.

We retrospectively reviewed the records of 141 consecutive patients with metastatic breast cancer identified from pharmacy records as receiving capecitabine outside of a clinical trial between May 1998 and February 1999...

It is apparent that the toxic effects associated with capecitabine therapy at 2,500 mg/m^2/day cause morbidity in a relatively high proportion of patients, necessitating frequent dose reduction. This is consistent with our experience. Since the most important goal of the treatment of metastatic breast cancer is symptom palliation, therapy associated with considerable morbidity defeats the purpose. Reduction of the capecitabine dose has been shown to improve drug tolerability in most cases.

Moreover, retrospective analysis of many of the capecitabine trials has found that dose reduction for adverse events related to capecitabine did not have an impact on efficacy of the drug. This is supported by our data. In our experience, the mean tolerated dose of capecitabine is 2,040 mg/m^2/day. Thus, it seems appropriate to use the drug at a lower starting dose, perhaps 2,000 mg/m^2/day in two divided doses.

Bajetta E et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol 2005;23(10):2155-61.

To the best of our knowledge, this is the first report specifically dealing with the use of capecitabine in an elderly population with breast cancer...

Overall, efficacy of the two starting doses was similar to that reported in a previous trial, in which first-line monotherapy with capecitabine at the dose of 2,500 mg/m^2/d resulted in an objective response rate of 30% in 61 women aged 55 years and older. This study has shown in a large series that oral capecitabine is well tolerated and effective in older women with advanced breast cancer. Older patients may frequently exhibit diminished capacity to eliminate drugs, resulting in unusual sensitivity to standard dosing regimens.

In light of this, the overall results of the study suggest that although the dose groups are small and nonrandomized, the capecitabine dose of 1,000 mg/m^2 twice daily merits consideration as "standard" for women aged 70 years and older who are candidates to cytotoxic therapy for metastatic breast cancer and do not have severely impaired renal function.

Meet The Professors 2005 (3)

DR O'SHAUGHNESSY: I have been impressed with the combination of a taxane and capecitabine in patients with the bone and liver metastases.

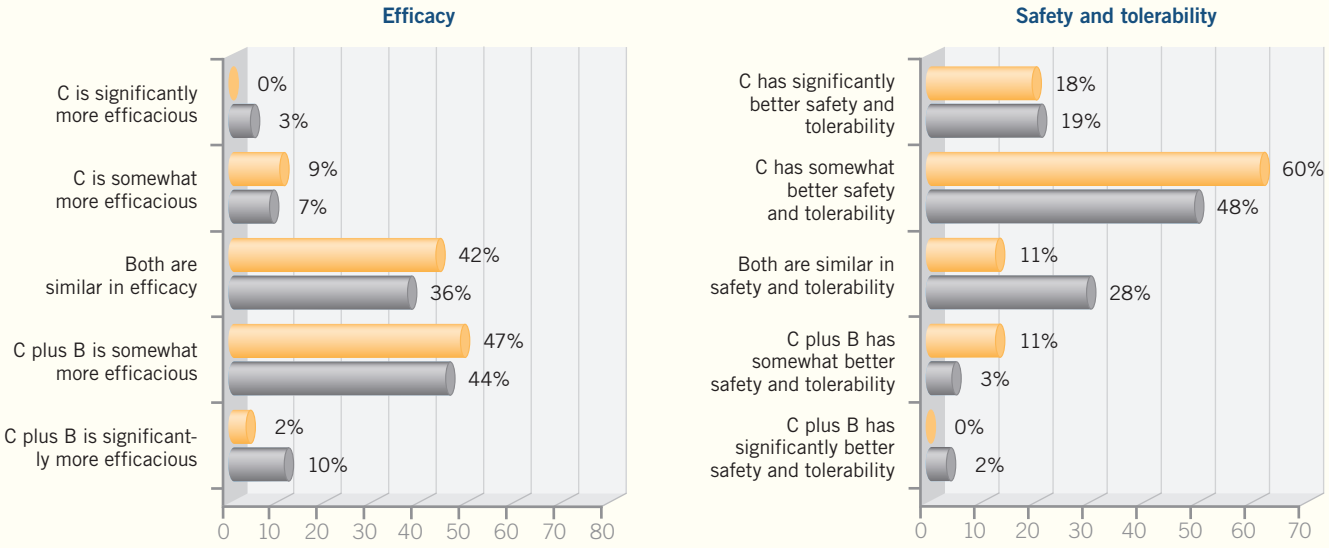
I think the capecitabine dose of 825 mg/m^2 BID, 14 days on and seven days off, is now pretty well established for combination therapy. I will usually treat for six or seven cycles with the combination, stop the taxane and keep going with capecitabine. The duration of response that I have seen with some patients has been remarkable. That is not to say that you wouldn't have seen the same if you had used sequential therapy, but the duration of responses in a number of patients is impressive, and it's gratifying.

In the *JCO* an Italian group reported a Phase II first-line metastatic trial of capecitabine in patients with a mean age of 73. Patients were started on capecitabine at 1,250 mg/m^2 BID. Two deaths occurred, so they reduced the dose to 1,000 mg/m^2. The report included about 40 patients treated with 1,250 mg/m^2 and another 43 patients treated with 1,000 mg/m^2. In the trial, they observed an acceptably low rate of Grade III toxicities with the lower dose

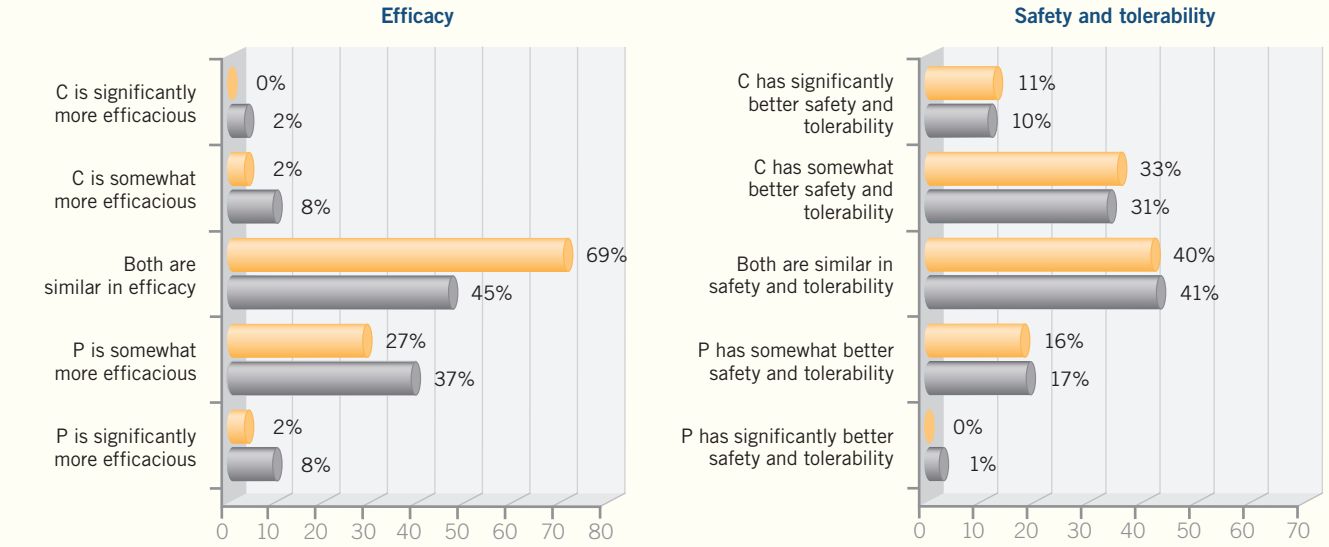
FIGURE 51

*For a patient who presents with asymptomatic metastatic disease and no prior systemic therapy, how would you generally compare the following?**

Capecitabine (C) versus capecitabine plus bevacizumab (B)



Capecitabine (C) versus paclitaxel (P)

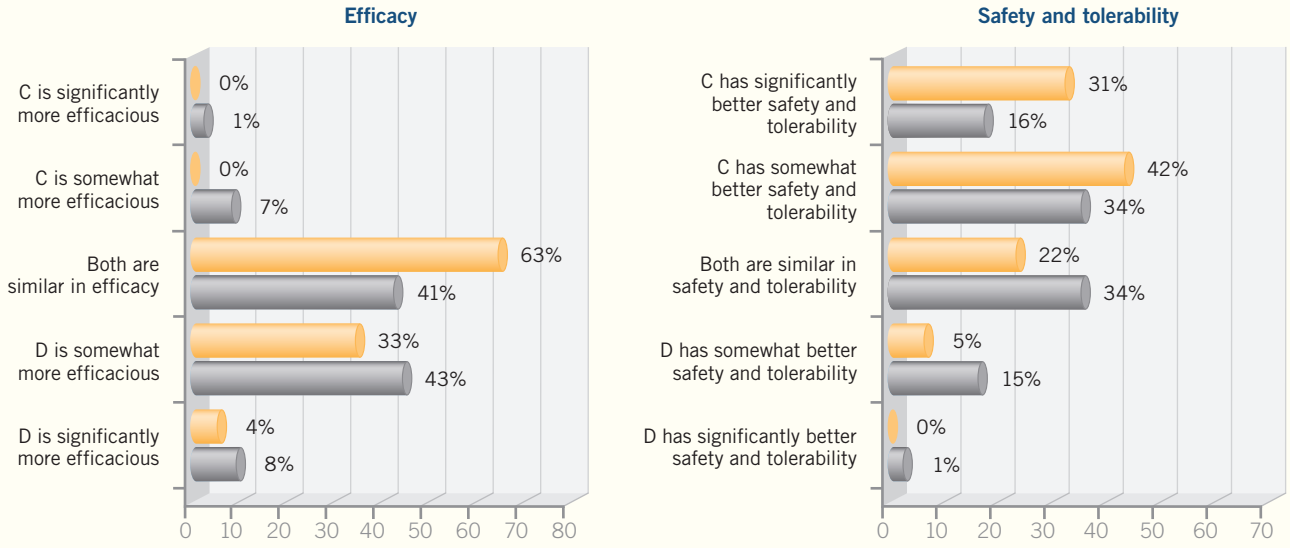


* n = 45 clinical investigators and 134 community oncologists who use capecitabine

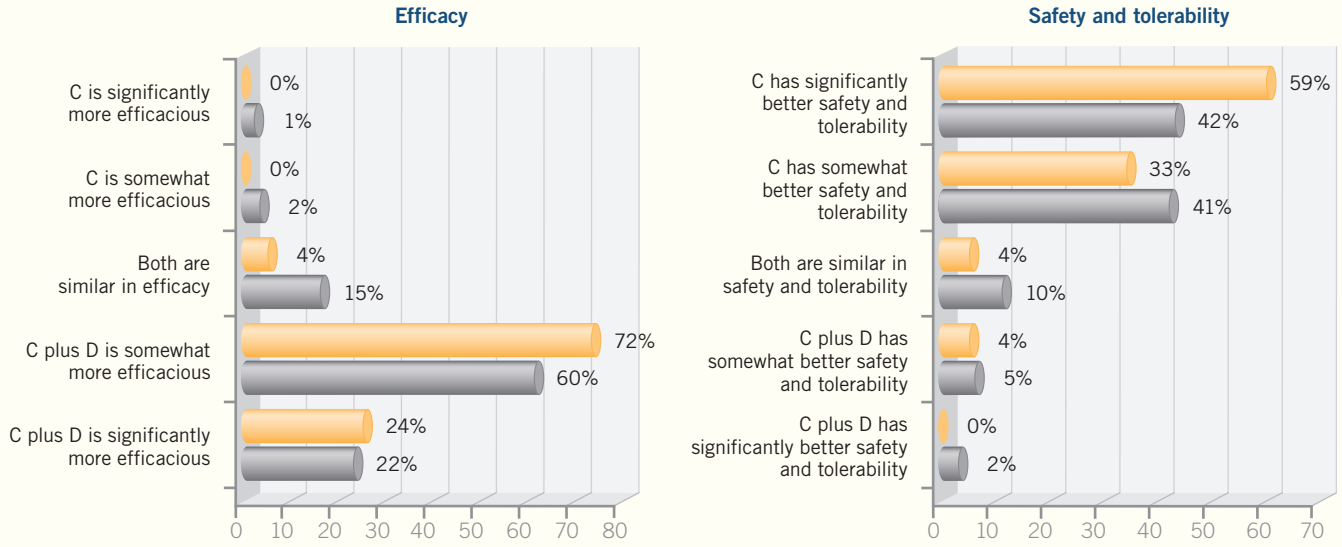
FIGURE 51 (CONTINUED)

*For a patient who presents with asymptomatic metastatic disease and no prior systemic therapy, how would you generally compare the following?**

Capecitabine (C) versus docetaxel (D)



Capecitabine (C) versus capecitabine plus docetaxel (D)

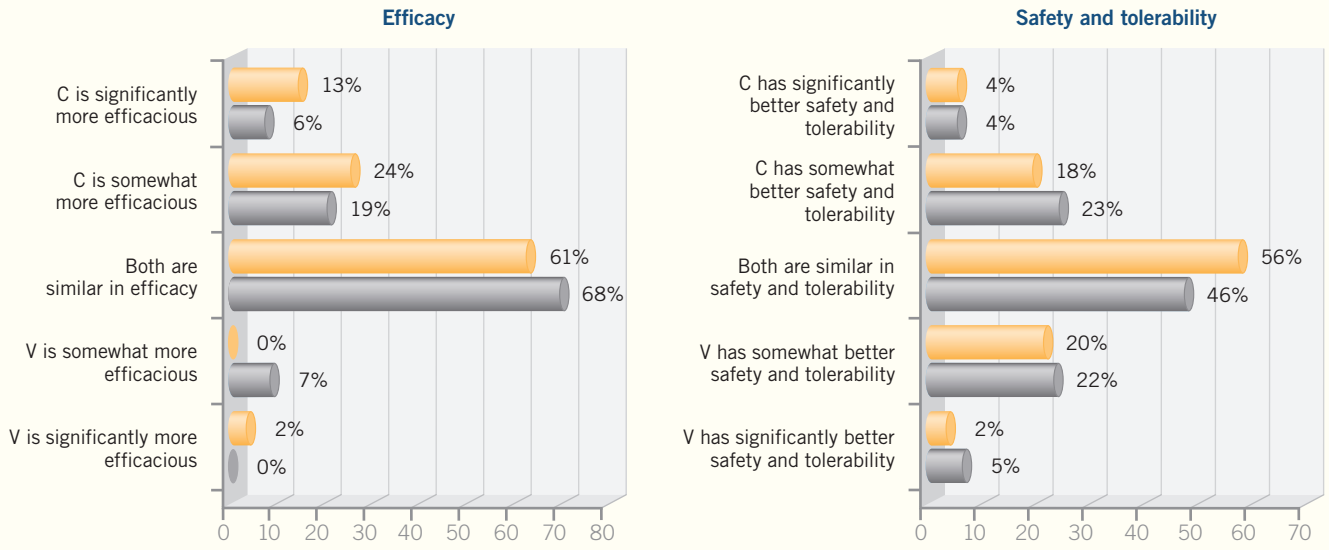


* n = 45 clinical investigators and 134 community oncologists who use capecitabine

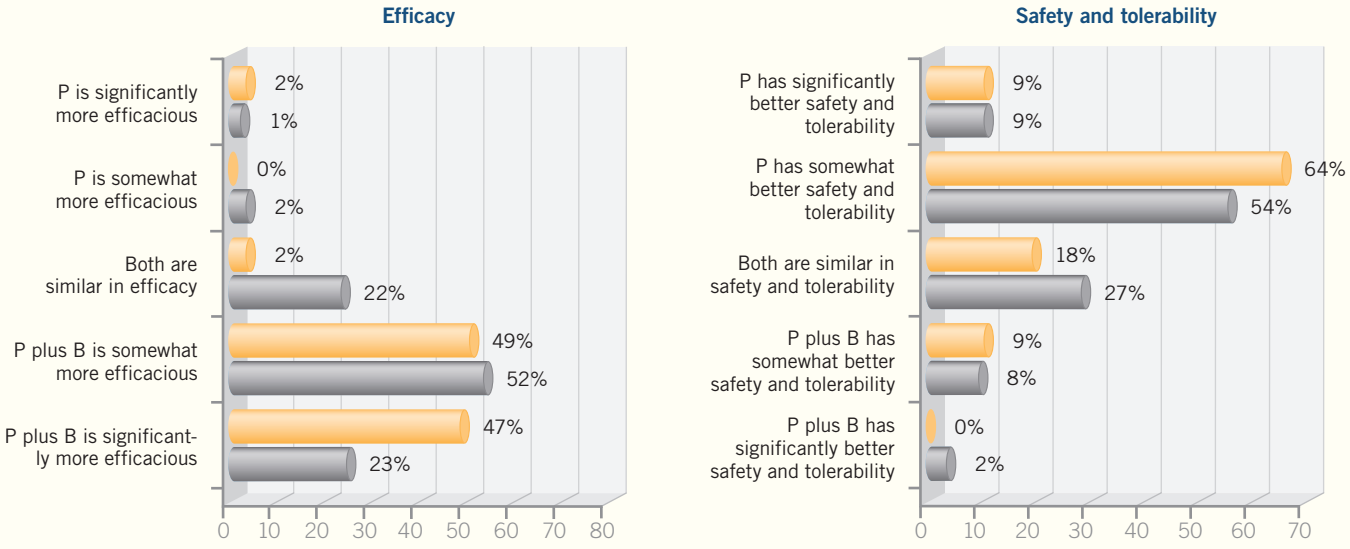
FIGURE 51 (CONTINUED)

*For a patient who presents with asymptomatic metastatic disease and no prior systemic therapy, how would you generally compare the following?**

Capecitabine (C) versus vinorelbine (V)



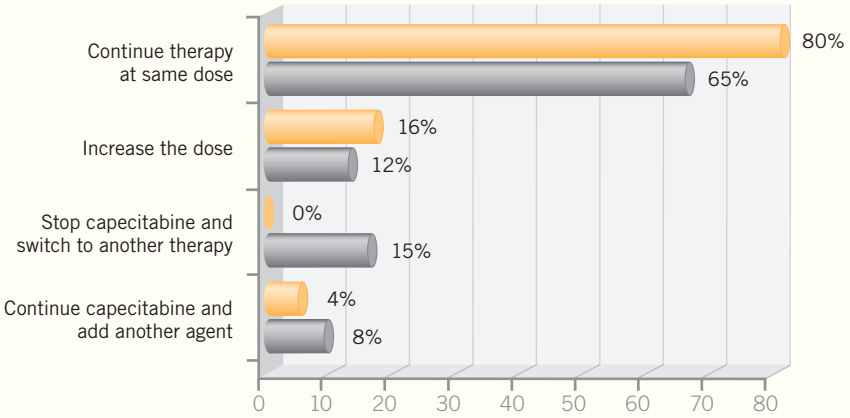
Paclitaxel (P) versus paclitaxel plus bevacizumab (B)



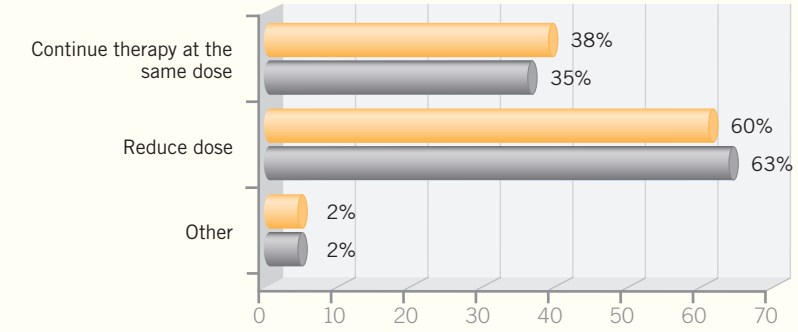
* n = 45 clinical investigators and 134 community oncologists who use capecitabine

FIGURE 52

*Assume that you are presented with a breast cancer patient who is 55 years old with asymptomatic lung mets and has been started on capecitabine, 2,000 mg/m^2 in two divided doses of 2 weeks on then 1 week off. After 3 cycles, she has had no changes in the lesions and no side effects. Which of the following best describes what you would generally do?**



*Same as above but after 3 cycles, she is having an objective response in the lungs but complains of mild pain and redness in her hands and feet. Which of the following best describes what you would generally do?**



* n = 45 clinical investigators and 134 community oncologists who use capecitabine

in less than 10 percent of patients. In both cohorts, the response rate was 35 percent, which is pretty impressive, and another third of patients treated with 1,000 mg/m^2 had stable disease for more than six months. That is getting remarkably high.

Meet The Professors 2005 (3)

DR HUDIS: I don't harbor a firm belief that the order of single agents matters as much as people believe it does. For patients reluctant to receive chemotherapy for reasons that are largely emotional, capecitabine allows them to make that transition and say to themselves, "I'm not getting intravenous therapy. It's not so bad."

The fact that capecitabine is as active as many of the intravenous therapies that we routinely use makes this sort of a silly point, but it is one that people buy into. So if I have a patient who is reluctant to start intravenous therapy, I will look toward capecitabine.

If I have an older patient, to tell you the truth, it cuts both ways. The truth is that capecitabine does bring up compliance and safety issues related to self-administration. It's not crystal clear to me that it's always safe for or better for a person to take medication at home. Sometimes you have a little more control over them if you can administer intravenous therapy and withhold it when you should.

Breast Cancer Update 2005 (5)

DR NANCY E DAVIDSON: Many times in metastatic disease we use all of the available therapies, so what we're really deciding on is the order — what to start with. Many patients make that decision based on their personal values. I find many of my older patients are attracted to capecitabine because it is an oral agent. Some of my younger patients think of intravenous therapy as more aggressive, and they prefer that strategy.

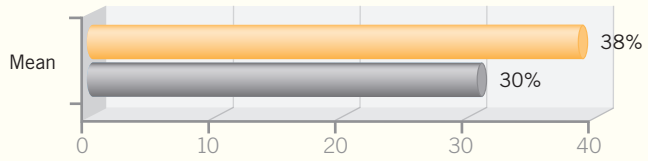
However, this perception is based on gut reaction rather than reality. I am a big fan of capecitabine. Maybe it comes from being a "hormonal therapy person" who prefers pills to begin with because I use capecitabine a lot for salvage chemotherapy in women who have already had an anthracycline and a taxane for metastatic disease. In oncology, we tend to remember our successes, but I have seen several impressive responses with capecitabine in dire circumstances. I have had women on capecitabine for a considerable period of time with relatively good quality of life.

Breast Cancer Update 2005 (9)

DR VOGEL: In postmenopausal patients, when I use hormonal therapy in metastatic disease, for the most part, I generally start with an aromatase inhibitor. There are nine lines of hormonal therapy for postmenopausal women, and there is no tried and true sequence — we don't have any consensus on a true hormonal cascade. In some women hormones can be manipulated for years. I've had

FIGURE 53

*About what percentage of breast cancer patients treated with capecitabine in your experience have side effects requiring dose reduction?**

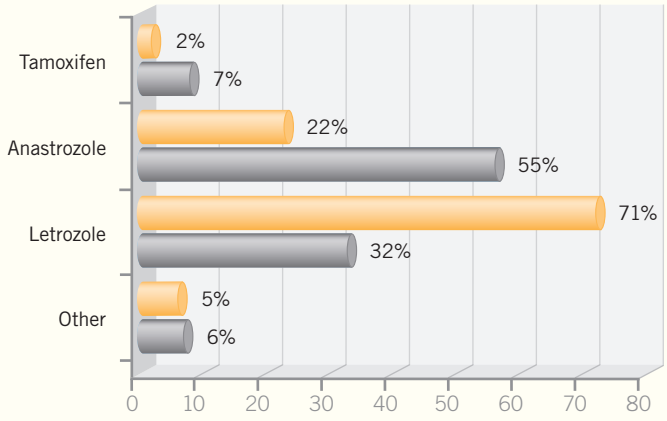


* n = 45 clinical investigators and 134 community oncologists who use capecitabine

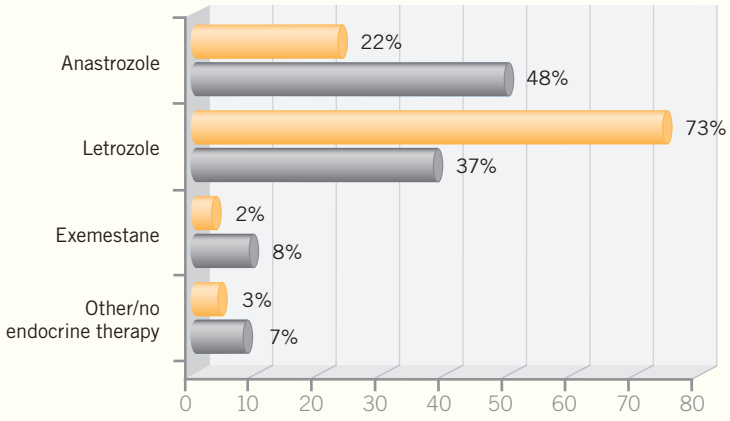
FIGURE 54

Which first-line endocrine therapy, if any, would you generally use in postmenopausal patients with metastases?

No prior endocrine therapy



Completed adjuvant tamoxifen four years previously



patients on hormonal therapy for 10 or 12 years before ever reaching cytotoxic chemotherapy.

Breast Cancer Update 2005 (4)

DR GRADISHAR: If you evaluate most of the available data with endocrine agents in the metastatic setting — tamoxifen, steroidal or nonsteroidal aromatase inhibitors or fulvestrant — the question that comes up is whether one sequence enhances patient outcome more than another. This becomes important because if you can demonstrate that one sequence enhances the time to disease progression, it may be built on over time so that overall outcome is improved.

In theory, simply having an improvement in recurrence or progression of metastatic disease impacts quality of life. Patients now typically receive a nonsteroidal aromatase inhibitor — anastrozole or letrozole — as the first treatment.

The question then becomes, if patients progress on one of those agents, what would be the next best therapy? Should it be the steroidal aromatase inhibitor exemestane, or should it be fulvestrant?

Indirect data evaluating the sequence of a nonsteroidal aromatase inhibitor to fulvestrant suggest that 25 to 30 percent of patients may benefit with that approach. An important issue is whether fulvestrant at 250 mg is optimal.

Some of the data suggest that the dose is really on the low end of the curve where you might expect the optimal response rate. Some strategies have evaluated quickly increasing serum levels of fulvestrant, including administering loading doses of 500 mg and within two weeks administering another 250 mg and then proceeding to the monthly schedule. Those strategies are based on mathematical modeling that has shown an ability to achieve steady-state levels much more quickly and consequently achieve a biologically relevant dose of drug circulating much faster.

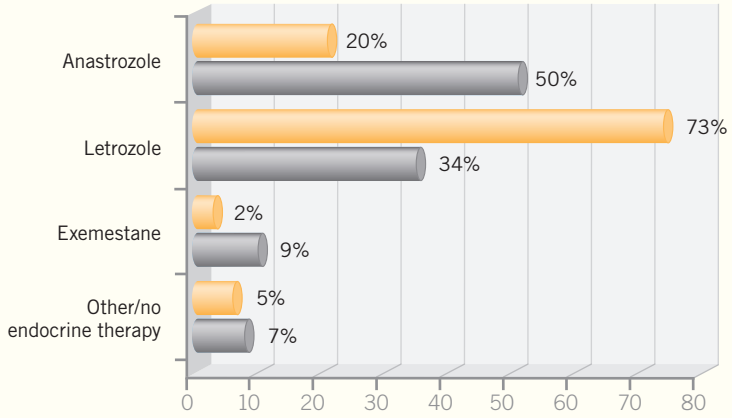
Patterns of Care 2005 (1)

DR JONES: Generally, patients are either going to relapse on tamoxifen or after

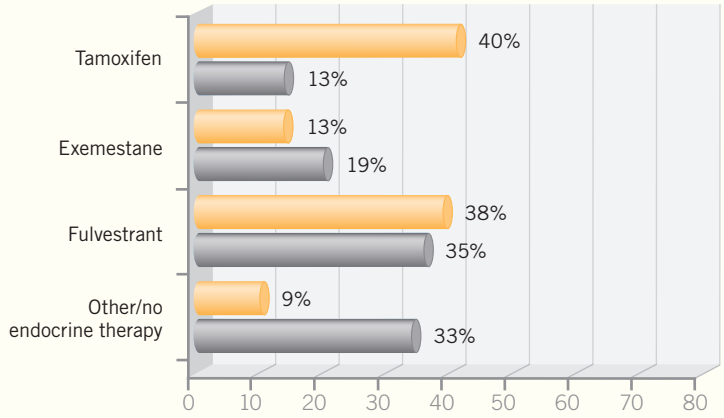
FIGURE 54 (CONTINUED)

Which first-line endocrine therapy, if any, would you generally use in postmenopausal patients with metastases?

Completed adjuvant tamoxifen one year previously



Completed adjuvant anastrozole one year previously



adjuvant tamoxifen. In that setting and in the fulvestrant versus anastrozole clinical trials, evidence exists that a proportion of women have a longer response to fulvestrant than to anastrozole when given right after tamoxifen. I've had patients with long responses to fulvestrant.

I prefer fulvestrant to an aromatase inhibitor after tamoxifen because approximately 20 percent of patients have long responses with it in this setting. However, 99 percent of oncologists will choose an aromatase inhibitor after tamoxifen. Fulvestrant is generally being used as third-line therapy.

Despite Trials 20 and 21, most physicians start with anastrozole rather than fulvestrant because of the way the data have been presented. We are just beginning to see patients who have been treated with two or three years of adjuvant anastrozole and then relapsed.

Currently, there are few data on treatment options in this setting. It's somewhat of a "dealer's choice" because there are no hard and fast rules. There are multiple options including fulvestrant, exemestane and even tamoxifen — if the patient hasn't seen it — because it's obviously still a useful drug. So the sequence is going to be all over the map for most folks.

Patterns of Care 2005 (1)

DR BURSTEIN: Previously, patients received tamoxifen in the adjuvant setting, so we would use an aromatase inhibitor as front-line therapy in the metastatic setting. Fulvestrant was used second line, or we could use megestrol acetate, but for many women fulvestrant has a more convenient side-effect profile.

Now that more women receive aromatase inhibitors in the adjuvant setting, we're using tamoxifen or fulvestrant as first-line treatment in the metastatic setting.

Breast Cancer Update 2005 (5)

DR DEBU TRIPATHY: In the up-front study, tamoxifen and fulvestrant were essentially equivalent. As second-line therapy, fulvestrant seemed to perform equally as well as anastrozole. At this point in time, the sequencing and timing for fulvestrant are unclear. I think it's reasonable to use the drug — maybe not up front, but as second- or third-line therapy.

This is when you might consider the patient's preferences in terms of an intramuscular or an oral drug. A recent study of 261 women with metastatic breast cancer demonstrated that about one third preferred a monthly intramuscular injection. I've always assumed that oral drugs were preferable, if they were equally effective. Therefore, I was surprised to see that many patients preferred an intramuscular injection. I need to query my patients more when I start evaluating these options.

Patterns of Care 2005 (1)

DR JOANNE L BLUM: In my experience, patients tolerate the fulvestrant injections just fine. We have randomized data comparing fulvestrant versus anastrozole in patients who have already received tamoxifen, but the optimal sequence for using fulvestrant is still undetermined. In

FIGURE 55

Which first-line endocrine therapy, if any, would you generally use in progression after 4 years of adjuvant anastrozole?

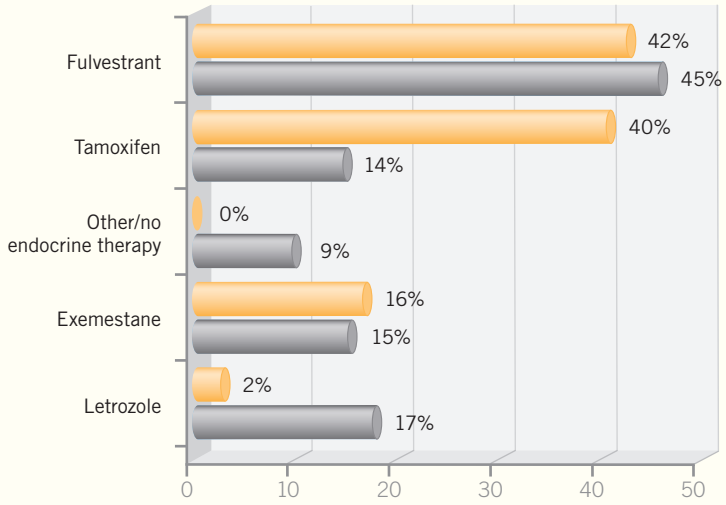
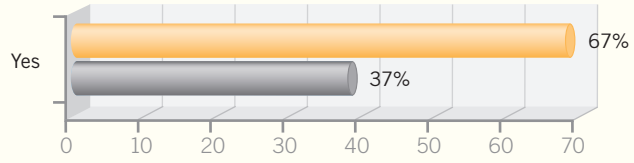


FIGURE 56

*When utilizing fulvestrant in the metastatic setting, do you generally use a loading dose?**



* n = 45 clinical investigators and 132 community oncologists who use fulvestrant

choosing between an aromatase inhibitor and fulvestrant, I ask my patients whether they prefer an injection or a pill. If they have transportation problems, then I use an oral agent.

However, for the Medicare population, these drugs are very expensive. If the patient does not have adequate insurance coverage and can't afford them, a monthly injection may be better. Compliance is also an issue to be considered when choosing between a daily oral agent and a monthly injection.

Special Edition BCU: Proceedings from Two Medical Oncology Educational Forums, 2005

DR OSBORNE: Two clinical trials were conducted comparing fulvestrant versus anastrozole for second-line therapy in patients who had received tamoxifen in the adjuvant or metastatic setting. One study was conducted in North America and the other in Europe and the rest of the world. The data from both trials were similar. The complete response rate was slightly higher with fulvestrant, whereas the partial and objective response rates were similar.

In terms of stable disease and clinical benefit, fulvestrant was a tiny bit better than anastrozole. In one of the trials, duration of response favored fulvestrant, but by and large, the drugs were similar.

How does fulvestrant compare with tamoxifen in the front-line setting? All the preclinical data suggested that fulvestrant would be significantly better than tamoxifen, so a trial was conducted comparing these two endocrine agents. In the receptor-positive group, fulvestrant and tamoxifen were similar in response and time to treatment failure, but overall, tamoxifen looked slightly better in some of the parameters.

Breast Cancer Update 2005 (8)

DR VALERO: Our approach in the institution is to use an aromatase inhibitor up front and then fulvestrant as second-line therapy. Fulvestrant is approved for patients who have failed tamoxifen, so you can use one agent or the other.

In the palliative setting, I believe you can use it either way. Fulvestrant has been shown to be as effective as anastrozole and tamoxifen. I use them in sequence. I don't believe there is any information that one sequence is better than the other. I use an aromatase inhibitor, and then I use fulvestrant as a second-line therapy.

Breast Cancer Update 2005 (8)

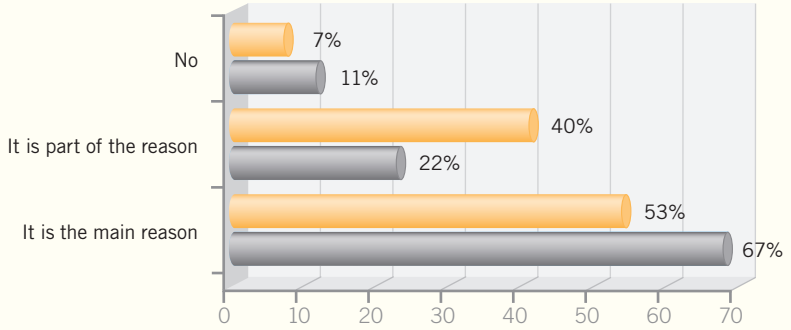
DR BUDD: I tend to use an aromatase inhibitor first and then use fulvestrant. One could build a rationale for using an alternative sequence, but I believe the data for aromatase inhibitors are strong.

When trying to decide between fulvestrant and an aromatase inhibitor for a postmenopausal patient who has relapsed on adjuvant tamoxifen, I believe ease of administration and the magnitude of the information are key. We have trials with each one of these agents that indicate, in one way or another, that the aromatase inhibitors are an optimal treatment. Granted, anastrozole and fulvestrant appear to be equivalent in that situation. So fulvestrant is also a reasonable choice.

I believe most, but not all, patients would still rather take a pill than have an intramuscular injection. Many of these patients are coming back to the clinic on a monthly basis for a bisphosphonate, so

FIGURE 57

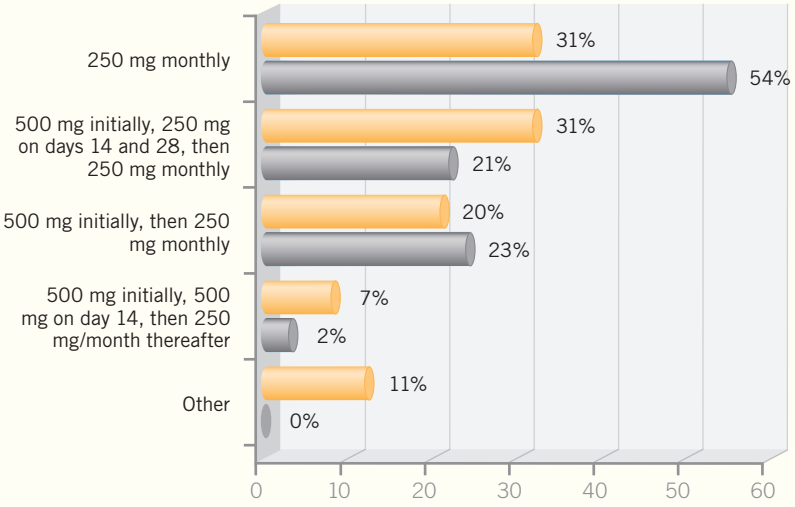
*If you do not generally use a loading dose, is cost and reimbursement the primary reason?**



* n = 15 clinical investigators and 101 community oncologists who do not use a loading dose

FIGURE 58

*Which of the following best describes how you dose fulvestrant?**



* n = 45 clinical investigators and 132 community oncologists who use fulvestrant

some of the practical advantages of a pill may not pertain for all patients.

Breast Cancer Update 2006 (3)

DR JOHN FR ROBERTSON: The SoFEA trial compares exemestane to fulvestrant following another aromatase inhibitor. The EFECT study is also testing exemestane versus fulvestrant following another aromatase inhibitor. That study has finished recruiting and is now in the follow-up phase, so the results should be reported in the foreseeable future.

With the SoFEA trial, I hope we see an improvement by combining the two treatments, though I suspect we may have answers to that question before the SoFEA trial results are reported, in that metastatic studies often take a bit longer to run. A couple of ongoing studies are also combining therapies, and they may report sooner.

The SWOG-S0226 trial is comparing fulvestrant with anastrozole to anastrozole alone, so we may see whether the combination is better than a single-agent aromatase inhibitor, and that will be an interesting result.

Breast Cancer Update 2004 (6)

DR MITCHELL DOWSETT: EFECT is an American and European study that randomly assigns patients who have failed therapy with a nonsteroidal aromatase inhibitor to fulvestrant or exemestane.

Our own study, SoFEA, is slightly different from EFECT because it is based on the observation that the addition of small amounts of estrogen to cells that have been estrogen deprived for a long time reduces the effectiveness of fulvestrant. That scenario equates to the withdrawal of a nonsteroidal aromatase inhibitor and the addition of fulvestrant.

Hence, the third arm of our trial includes a nonsteroidal aromatase inhibitor and fulvestrant. I predict fulvestrant alone will probably be better than exemestane, and fulvestrant with anastrozole will be better than fulvestrant alone.

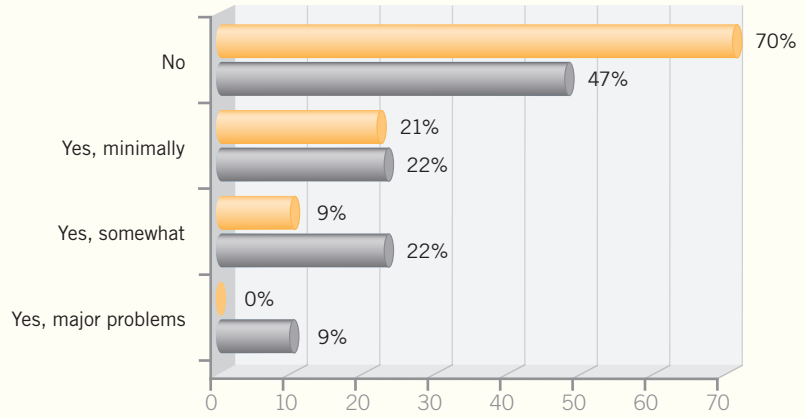
Breast Cancer Update 2005 (9)

DR VOGEL: In terms of efficacy, fulvestrant seems to be equivalent to anastrozole. Based on data published this year in *Cancer*, there seems to be no difference in overall survival in the randomized trials of anastrozole versus fulvestrant.

Fulvestrant is a good drug and a viable alternative to aromatase inhibitors in patients who have disease progression on tamoxifen. We do have to contend with the randomized trial of fulvestrant versus tamoxifen, where we expected a strongly beneficial effect for fulvestrant over tamoxifen, which was not forthcoming. There were some subsets where fulvestrant appeared to be better, but the overall results were about the same.

FIGURE 59

*Have you had problems with reimbursement for the loading dose of fulvestrant?**



* n = 33 clinical investigators and 86 community oncologists who have used a loading dose of fulvestrant

Breast Cancer Update 2005 (8)

DR VALERO: At MD Anderson we use a loading dose of fulvestrant. We administer 500 milligrams on day one and 250 milligrams on day 15 and day 29, and then monthly. Many of the key investigators in the early development of the drug believe it is important to attain steady state. As you know, there are no randomized data for the loading approach.

Currently, it is FDA approved at 250 milligrams monthly and is reimbursed by Medicare at that dose. With all of those caveats, I believe — and I don't know if this is my bias — the loading approach is reasonable.

Meet The Professors 2005 (6)

DR AMAN U BUZDAR: Data suggest that if you use the package insert dose of fulvestrant, which is 250 mg every four weeks, it takes about two to three months to get a steady-state therapeutic level. So we give a 500-mg loading dose, and then in another two weeks we give another 250 mg, and then treat every four weeks.

This is being evaluated in a prospective study because an important question is whether we are losing some patients before we get to the therapeutic level and the disease is progressing because patients do not have enough drug in their system.

Breast Cancer Update — Think Tank Issue 1, 2006

DR ROBERTSON: There is evidence supporting a loading dose of fulvestrant. First, tamoxifen reaches a steady state at two weeks, whereas fulvestrant can take up to four or five months to reach a steady state.

Another issue, which I believe makes people slightly uncomfortable, is that in the second-line study, fulvestrant was just as good as anastrozole after tamoxifen.

The first-line study, however, had two problems. Although it was a randomized study, 10 percent more people were assigned to fulvestrant than tamoxifen.

In addition, in the intention-to-treat population, the time-to-progression curve for the initial fulvestrant arm drops down much more quickly than the curve for tamoxifen, and then, after the first six months, it runs parallel to tamoxifen. It makes one think that perhaps the drug is not on board in that first six months.

The question is, why would you see this in the first-line and not the second-line setting? You could argue that some of those patients in the second-line setting may be having a tamoxifen withdrawal effect while the fulvestrant levels are going up.

Breast Cancer Update 2005 (8)

DR VOGEL: Although we think that may be utilizing the best dosing schedule for fulvestrant, we won't know unless we do a pharmacokinetic study and a large study to show that the doses are equally effective. I'm not sure if we're going to be seeing a dosing study large enough to determine efficacy. You can look at the pharmacokinetics in a smaller study, but I don't know if we're going to see efficacy differences.

Fulvestrant is a good drug that has minimal toxicity. We don't even encounter much in the way of buttock pain with a five-cc injection. We're also not seeing the degree of joint discomfort that we see with the aromatase inhibitors.

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

- Compare and contrast management strategies of community oncologists and cancer research leaders for the treatment of breast cancer in the adjuvant and metastatic settings. 5 4 3 2 1
- Discuss cancer management issues for which relative agreement and heterogeneity exist in patterns of care. 5 4 3 2 1
- Counsel cancer patients about multiple acceptable treatment options when they exist. 5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

Related to my practice needs. 5 4 3 2 1

Will influence how I practice 5 4 3 2 1

Will help me improve patient care 5 4 3 2 1

Stimulated my intellectual curiosity 5 4 3 2 1

Overall quality of material. 5 4 3 2 1

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

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Patterns of Care in Medical Oncology

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: NLove@ResearchToPractice.net
FOR CME INFORMATION	Email: CME@ResearchToPractice.net

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