2004 . Vol 1. Issue 1

Patterns of Care in Medical Oncology

Management of Breast Cancer in the Adjuvant and Metastatic Settings

Adjuvant Chemotherapy

Adjuvant Hormonal Therapy

Choice and Use of Taxanes

Endocrine Therapy in the Metastatic Setting

HER2 Testing and Trastuzumab

Extraordinary Cases

Editor: Neil Love, MD

CME Certified

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Breast Cancer™ UPDATE

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STATEMENT OF NEED/TARGET AUDIENCE

Medical oncology is one of the most rapidly evolving fields in medicine. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care, the practicing medical oncologist must be well-informed of these advances and aware of the ever-expanding spectrum of options available to treat their patients.

It is also 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 research leaders. While there is often agreement, it is important for oncologists to recognize the heterogeneity that exists in the oncology community, especially in clinical situations for which there is suboptimal existing 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 is research leader commentary and references addressing these issues. This CME program will provide medical oncologists with information on national cancer patterns of care in order to assist with the development of clinical management strategies.

GLOBAL LEARNING OBJECTIVES FOR THE *PATTERNS OF CARE* SERIES

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

- Compare and contrast a management strategy for the treatment of cancer patients to that of other community oncologists and cancer research leaders.
- Discuss cancer management issues for which there is relative agreement and those for which there is heterogeneity in patterns of care.
- Counsel cancer patients about multiple acceptable treatment options when they exist.

PURPOSE OF THIS ISSUE OF *PATTERNS OF CARE*

The purpose of this issue of *Patterns of Care* is to support these objectives by offering the perspectives of 150 randomly selected medical oncologists interviewed in-depth in March of 2004 regarding their practice patterns in the management of breast cancer.

HOW TO USE THIS MONOGRAPH

This monograph is the first issue of a CME series activity. To receive credit for this issue, the participant should read the monograph and complete the evaluation located in the back of this book or on our website **BreastCancerUpdate.com/POC**.

This monograph contains data from a national patterns of care survey of oncologists with related commentary from breast cancer research leaders and supplemental references. PowerPoint files of the graphics contained in this document can be downloaded at **BreastCancerUpdate.com/POC**.

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Patterns of Care: A CME Series Activity

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Neil Love, MD
Course Director/Editor
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Any procedures, medications or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information and comparison with recommendations of other authorities.

Pharmaceutical agents discussed in this program

Generic	Trade	Manufacturer
aminoglutethimide	Cytadren®	Novartis Pharmaceuticals
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cisplatin	Platinol®	Bristol-Myers Squibb Company
clodronate	Not FDA-Approved	—
cyclophosphamide	Cytoxan® Neosar®	Bristol-Myers Squibb Company Pfizer Inc
dexamethasone	Various	Various
doxorubicin	Adriamycin® Rubex®	Pfizer Inc Bristol-Myers Squibb Company
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
epirubicin hydrochloride	Ellence®	Pfizer Inc
epoetin alpha	Procrit® Epogen®	Ortho Biotech Products LP Amgen Inc
exemestane	Aromasin®	Pfizer Inc
filgrastim	Neupogen®	Amgen Inc
fluorouracil (5-FU)	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly and Company
goserelin acetate	Zoladex®	AstraZeneca Pharmaceuticals LP
letrozole	Femara®	Novartis Pharmaceuticals
megestrol acetate	Megace®	Bristol-Myers Squibb Company
methotrexate	Various	Various
nab-paclitaxel	Abraxane™	American Pharmaceutical Partners, Inc
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pamidronate disodium	Aredia®	Novartis Pharmaceuticals
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Introduction

Editor's note: Labor and delivery

Pregnancy and childbirth have always impressed me because of the profound demands placed on the mom-to-be and the highly variable nature of the outcome. The mothers of Einstein, Marcus Garvey and Attila the Hun all followed the same basic pathway and had varying results. So it is with developing a new continuing medical education (CME) program. Conception is the fun part; making it happen is another story. This innocent-appearing periodical is actually an experiment in progress that has driven half of our staff insane with our very frequent changes to the prototype made along the way.

Essentially, the idea of *Patterns of Care* is simple. (Our staff also fought bitterly over the title, with their camp campaigning for "*Choices*.") We wish to obtain input from a variety of sources about how patients with cancer are actually managed in community-based practice, and then juxtapose those findings with research leaders' comments from our CME audio programs and meetings.

This may sound simple, but it is surprisingly challenging to accomplish. The first three issues of this endeavor — forthcoming between now and December — target breast cancer, but we expect and hope to complete future issues about other tumor types. Our approach to gathering data is simple and is one we have been refining for more than 15 years. Essentially, medical oncologists, randomly selected from mailing lists of professional organizations, were asked to participate in a telephone survey in exchange for a modest honorarium. In addition to the usual hypothetical case-based questions, like "How would you treat a patient with…?" we also asked these 150 physicians to describe de-identified cases from their practices in an attempt to better assess their management of patients with breast cancer.

We also asked each physician to describe one of their patients with metastatic breast cancer who had experienced an unusually good response to systemic therapy, and we have included some of these "extraordinary cases" in the Appendix. We often hear about such patients from research leaders and thought it would also be interesting to query community-based practitioners about any similar experiences. Our intent is not to overstate the benefits of systemic therapy, but rather to recognize that while patients with metastatic breast cancer are, perhaps, not "curable," some may experience responses that are rare or unseen in many other solid tumors.

Our goal for this first pilot survey was to evaluate as many management issues as possible in order to generate hypotheses we could test more definitively in the next two surveys. Therefore, we designed three different tandem questionnaires and divided the 150 medical oncologists into three equal groups. This methodology left us with some substantial statistical variation, but also provided us the opportunity to refine the wording of the questions and the data collection process. In other words, this was a learning experience.

We are also not addressing every possible issue in this complex illness but rather focusing on some of the most controversial and important issues in breast oncology that continually emerge in our CME needs assessment activities.

Most of the results we obtained from these pilot surveys are believable, but some warrant closer study, particularly when inconsistencies are noted. On the other hand, doctors in practice can and do make decisions that perhaps most research leaders would not. Most of these options are evidence-based, but it is curious how uniform research leaders are in their management paradigms — particularly compared to community-based practitioners.

For example, with the oncologist's permission, I listened to a tape of one of the first anonymous surveys. This very intelligent and well-read physician knew the breast cancer literature inside and out. When asked to describe the last postmenopausal woman in his practice with an ER-positive, node-positive tumor who had recently completed adjuvant chemotherapy, he discussed a very healthy, active woman in her mid fifties with two positive nodes.

Thinking back to our *Breast Cancer Update* audio program, I would guess at least 90 percent of the research leaders interviewed would use a taxane in such a patient, and three-fourths would use dose-dense AC followed by T. This particular physician had prescribed four cycles of AC. Perhaps he had visualized absolute risk reduction figures in which the added toxicity of a taxane was not worth the incremental benefit. Perhaps he would change his approach to such a patient if he heard 10 research leaders suggest a taxane. Perhaps the 10 researchers would change their minds if they were exposed to this community physician's thought process about this particular woman. We will address these and other questions in future issues.

The bottom line can be summarized in two words: "Stay tuned." By the end of the year, we will have a better idea of where things are and maybe where they need to go in breast cancer management. Hopefully, the fruits of this labor will be interesting and provocative.

— Neil Love, MD
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FIGURE 1

Demographics

What fraction of your work is patient care?

	Fraction of physicians
70-80%	6%
81-90%	21%
91-99%	35%
100%	38%

FIGURE 2

Demographics

Years in practice	15.3 years
Percent of patients in HMOs	27%
Percent of overall practice that is breast cancer (BCA)	33%
New BCA patients per month	13.5
BCA patients started on adjuvant therapy per month	9.3
Number of patients per month starting or switching systemic therapy for metastases per month	8

EDITOR'S COMMENT

The medical oncologists recruited for this survey were randomly selected from the national mailing list utilized for the Breast Cancer Update *audio series. These physicians spend the vast majority of their time in direct patient care.*

On average, these physicians have been in practice for 15 years. Approximately one-fourth of their patients have HMO insurance coverage, and about one-third have breast cancer — the largest patient segment in contemporary oncology. These physicians make important breast cancer treatment decisions an average of three to four times a week — both the initiation of adjuvant systemic therapy and starting or switching systemic therapy for metastatic disease.

Related Comments from Research Leaders

One of our major goals is to fully educate our patients by giving them relevant, accurate and complete information so that they understand their prognosis, treatment options and the benefit-to-risk ratio they will face with each of those options — but we can't stop there.

We also need to make a recommendation after that education. Obviously this recommendation will incorporate our biases and prejudices, but we are better qualified — even with those biases and prejudices — than a patient who just had "Oncology 101" during the previous 20 to 30 minutes. I feel very strongly about that.

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

I understand and agree that patients need to have autonomy. We clearly have the obligation to inform them fully, but I think we need to go beyond that.

We have to get to know our patients and understand their motivations, their understanding of risks and benefits, their definition of therapeutic gain and their acceptable level of risks and side effects.

As physicians, we need to help them make a decision. To abrogate that responsibility is an unfortunate — and I hope temporary — trend in the medical profession.

— Gabriel N Hortobagyi, MD

Medical treatment decisions in early as well as advanced breast cancer follow established guidelines clearly defined by consensus statements, meta-analyses, and evidence-based insights into the biology of the disease, and treatment efficacy.

Nevertheless, to treat patients "holistically" while remaining mindful of individual characteristics, physicians must consider patients' concerns regarding the course of their disease, their distress, and, in advanced disease, their knowledge of a limited life expectancy when making treatment choices. Such considerations will contribute to a more satisfactory patient-physician relationship and superior quality of life.

— Zielinski CC. Semin Oncol 2003;30(2 Suppl 3):27-9.

FIGURE 3

Participation in Breast Cancer Research

Do you enter patients in clinical trials?

No	27%
Yes	73%

For those answering "yes," what type of trials?

Cooperative Group	68%
Industry	52%

How many patients a year do you enroll in trials?

Mean	10.5

EDITOR'S COMMENT

Approximately three-fourths of oncologists enter patients in clinical trials, including both cooperative group and industry studies. Other surveys and keypad polling at meetings have suggested that the most significant impediment to clinical trial participation has been inadequate reimbursement and the amount of time and office support staff required for participation.

Related Comments from Research Leaders

Barriers to clinical trial accrual are multifactorial, and the Cancer Trials Support Unit (CTSU) was designed to attack several of them. Having the infrastructure support — the research nurse support, the IRB support and the financial support — to actually carry out the research is critical when deciding, especially in community practice, to participate in clinical trials. In addition, randomization can be a problem for some physicians and patients. While not able to handle all those issues, the CTSU was designed to reduce the burden of the regulatory paperwork.

For many physicians who choose not to participate in clinical trials, randomization is an issue. We, as physicians, feel that we know the right answer although, time and again, the trials have shown that we don't know the right answer or that our initial intuition isn't correct. Many physicians like to go with their bias or intuition and don't want to randomly assign patients to therapy. In addition, randomization takes more time on the part of the physician. They must explain the pros and cons, as opposed to just presenting a patient with a definitive treatment plan.

It takes a special type of physician who's willing to put biases aside and take the necessary time to explain why the choice of the therapy will be assigned randomly and why that makes sense in this situation. We always have a harder time when the trial is comparing a treatment to no treatment. The physicians who utilize a particular treatment are biased that the treatment will work.

— Jeffrey Abrams, MD

Arguably one of the most important advances during the last 50 years has been the introduction of prospectively randomized controlled trials to clinical medicine. Such trials provide information about the natural history of a disease and evaluate the worth of a particular therapy. Moreover, they allow for testing of biological hypotheses and, thus, provide a mechanism whereby the scientific method can be applied to clinical problem-solving. By replacing anecdotal information (which has influenced therapeutic decision-making in the past) with more credible and substantive data, clinical trials play a major role in transforming the practice of medicine from an art to a science.

As a vital component of the "research chain," clinical trials are an essential link between the laboratory and the clinic, providing means for determining whether the use of laboratory findings in the treatment of patients is justified. Without trials, much of the scientific information currently being reported could not be evaluated for its therapeutic worth.

— Bernard Fisher, MD
News from the Commision on Cancer of the American College of Surgeons 1991;2(2).

The randomised controlled trial has become the gold standard for evidence-based medicine; through the unbiased comparison of competing treatments it is possible to accurately quantify the cost-benefits and harm of individual treatments.

This allows clinicians to offer patients an informed choice and provides the data on which purchasing authorities can make financial decisions. We, of course, subscribe to this view but also recognize this as a gross over-simplification of the power of the randomised controlled trial. The randomised controlled trial is the expression of deductive science in clinical medicine.

Not only is it the most powerful tool we have for subjecting therapeutic hypotheses to the hazard of refutation, but also the biological fallout from such trials should allow clinical scientists to refine biological hypotheses. Trials of treatments for breast cancer have, at least twice, contributed substantially to a paradigm shift in our understanding of the disease.

— Michael Baum, ChM, FRCS;
— Joan Houghton, Bsc
Br Med J 1999;319:568-571.

FIGURE 4

Dose-Dense Adjuvant Chemotherapy

Have you read the report of CALGB-9741 in the 2003 Journal of Clinical Oncology*?*

No	44%
Read abstract, skimmed article	24%
Read entire article	32%

FIGURE 5

Adjuvant Aromatase Inhibitors

Have you read the report of the ATAC trial in the Lancet *or in the journal* Cancer*?*

No	85%
Read abstract, skimmed article:	
Lancet, 2002	10%
Cancer, 2003	8%
Read entire article:	
Lancet, 2002	10%
Cancer, 2003	4%

FIGURE 6

Sequencing of Aromatase Inhibitors and Tamoxifen in Early Breast Cancer

Are you aware of clinical trial reports of using aromatase inhibitors in postmenopausal patients completing five years of adjuvant tamoxifen?

Yes	100%
No	0%

Are you aware of clinical trial reports of switching to an aromatase inhibitor in postmenopausal patients on two to three years of adjuvant tamoxifen?

Yes	83%
No	17%

EDITOR'S COMMENT

One of the key factors in the extensive utilization of our audio series for oncology healthcare professionals has been the opportunity to "multitask" and listen while driving an automobile or (less frequently) while exercising. The challenge of keeping up to date with increasing demands on physician time is reflected in a finding related to CALGB-9741 — one of the most important clinical research databases reported in oncology in the last few years. Most physicians have stated that they heard about this study — which reported a significant benefit to dose-dense adjuvant chemotherapy — soon after it was presented by Dr Marc Citron in San Antonio in December 2002. However, one year after the formal publication of the paper on this landmark trial, only about one-half of oncologists recalled reading the article, and many had only read the abstract.

The initial results of the ATAC trial were presented by Dr Michael Baum at the December 2002 San Antonio Breast Cancer meeting. This study quickly shifted one of the most important paradigms in adjuvant endocrine therapy, and oncologists promptly heard about this landmark presentation through a variety of sources. However, the majority of oncologists have not read either of the two papers published on these findings. One likely explanation for this is that the journals in which these important papers were published — Lancet *and* Cancer *— are not as widely read by medical oncologists as the* Journal of Clinical Oncology.

At the time of the survey, two major papers published in the New England Journal of Medicine *reported a benefit for the adjuvant sequence of tamoxifen followed by aromatase inhibitors in postmenopausal patients. One paper, authored by Goss et al, focused on the use of letrozole versus placebo in women who had completed five years of adjuvant tamoxifen. The other study, reported by Coombs et al, demonstrated that women who had received two years of tamoxifen or switched to exemestane faired better than those who continued on tamoxifen. A previous trial reported by an Italian group at the 2003 San Antonio meeting demonstrated that women who had received two to three years of tamoxifen or switched to anastrozole fared better than those who continued on tamoxifen. Oncologists were well aware of this important emerging clinical research data.*

FIGURE 7

Clinical Use of Serum Tumor Markers

How frequently do you use tumor markers in women with...

	Metastatic disease	Postadjuvant therapy (node-positive)
Commonly	64%	48%
Occasionally	18%	12%
Rarely	8%	16%
Never	10%	24%

EDITOR'S COMMENT

ASCO has developed a set of guidelines regarding the use of tumor markers — such as CA 27.29 and CA 15.3 — suggesting that serial monitoring does not have a reliable research evidence base to justify this management practice. In contrast, many oncologists utilize this approach in both the post-adjuvant and metastatic settings.

Related Comments from Research Leaders

Although I generally agree with the American Society of Clinical Oncology (ASCO) guidelines that we should not be using markers because large studies have shown that they don't have a benefit, there are times when serial marker measurements may be appropriate. One example might be a patient with inflammatory breast cancer, when you have a suspicion that something is not right.

Another example would be the patient who is at very high risk for relapse. In these situations, we are hoping to diagnose the recurrence before it seriously threatens the patient's life or compromises a major organ system that would make it difficult to give therapy.

The rationale for seeing people every three to four months early in their disease and at greater intervals later is that early recurrences tend to be the most aggressive, and later recurrences tend to be more indolent. But some patients have such explosive disease that they should be followed more closely, particularly if something just doesn't add up, although I wouldn't do so in general.

— Peter Ravdin, MD

I'd like to speak for the physicians who do use tumor markers despite the ASCO guidelines. I use them routinely. You have to use a good deal of judgment, and there can be much discussion with patients. Such monitoring doesn't help all patients, but it does help some patients. In a small subset of patients, you pick up disease early and watch them more carefully.

This sometimes allows you to intervene with hormone therapy at a time when they're relatively asymptomatic. You may avoid situations in which patients get very sick very quickly and will need chemotherapy. It's very hard to show this value in randomized trials, but I've done it routinely over the past 15 years.

— Stephen E Jones, MD

Several randomized studies have evaluated whether a regular schedule of surveillance — imaging studies and tumor marker measurements — would help identify metastatic disease sooner and whether earlier initiation of therapy would improve survival time and quality of life. That strategy failed on both points.

If you do find the metastases earlier and initiate treatment earlier, it isn't going to extend life. All it's going to do is force me to tell a patient sooner that she has incurable metastatic disease. I don't see how that helps in any way, which is why I don't routinely measure tumor markers after adjuvant therapy.

Patients are often referred to me who've been having sequential tumor marker measurements that are rising. The patients undergo every kind of scan that can be done in search of metastatic disease, with tremendous costs and anxiety to the patient and family — and all the scans are negative. The patient is sent to me with the question: "What should we do?" My advice is quite consistent: "Stop checking the tumor markers."

— Kathy D Miller, MD

SELECT PUBLICATIONS

Bast RC Jr et al. **2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology.** *J Clin Oncol* 2001;19(6):1865-78. Abstract

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

Baum M et al. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial.** *Lancet* 2002;359(9324):2131-9. Abstract

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9. Abstract

FIGURE 8

Actual Cases from Physician Practices

Please describe the last postmenopausal patient recently completing adjuvant chemotherapy for a:

1. *Node-positive, ER-positive tumor*
2. *Node-negative, ER-positive tumor*

Patient profile	Node-positive	Node-negative
Age (median)	61	61
Number of positive nodes (median):	2	—
Tumor size (median)	2 cm	2 cm
HER2 status Negative Positive	 86% 14%	 84% 16%
Significant comorbid medical conditions	26%	18%

FIGURE 9

Actual Cases from Physician Practices

Did you use a computer program to calculate this patient's risk of recurrence?

Those who answered "yes" used:	Node-positive	Node-negative
ADJUVANT!	12%	26%
Mayo Clinic	10%	16%
Risk profile	**Node-positive**	**Node-negative**
Estimated baseline risk of relapse (mean)	40%	31%
Estimated risk of relapse with treatment (mean)	20%	17%
Physicians providing that information to the patient	76%	84%

EDITOR'S COMMENT

In many prior telephone surveys of physicians, we have posed theoretical case scenarios and asked oncologists how they might treat such patients. For this project, many similar questions were asked. However, we also added a new component in which physicians were queried about the last breast cancer patient they managed in very specific situations. The goal was to obtain "real world" insight into how patients are managed. The first two scenarios involved postmenopausal patients with ER-positive tumors who had recently completed adjuvant chemotherapy. We asked for one case of a patient with a node-positive tumor and another that was node-negative. The median age of 61 for these patients is lower than expected, perhaps reflecting a reluctance to use chemotherapy in older women. For patients with node-positive tumors, the median number of nodes was two, in keeping with the stage migration of breast cancer related to extensive use of mammographic screening. Note that a substantial number of treated patients had comorbid medical conditions that might have affected treatment decisions.

In recent years, two important computer web-based models have been developed to assist physicians in estimating the risk of recurrence and mortality in the adjuvant setting. Forty percent of physicians surveyed stated that they have used the Ravdin model and 21 percent have used the Mayo Clinic model. For these two cases, we found that the models were used more often in women with node-negative tumors, probably because the results were important in determining whether chemotherapy would be utilized. More than three-fourths of physicians stated that they provided this information to these patients. Note also that the estimated risk for relapse was similar in node-positive and node-negative cases, reflecting that only women with node-negative tumors at higher risk were likely to have been treated.

Related Comments from Research Leaders

The overview suggests that the proportional benefits hold up for a given therapy, irrespective of the baseline risk. If patients at low risk benefit 20 percent from a given therapy, patients at high risk receive a 20 percent relative benefit as well. So for the patient at low risk, a 20 percent benefit may be only one or two percent. But for the patient at high risk (50 percent), a 20 percent difference is a 10 percent risk reduction. This therapeutic index gets higher and higher with risk.

— Peter Ravdin, MD, PhD

The ADJUVANT! computer program (available at http://www.adjuvantonline.com) is based on nearly a decade

of work that originated with information from the San Antonio database. The underpinnings of Adjuvant! were based on the Surveillance, Epidemiology and End Results (SEER) database, a large population-based database with some great strengths. I believe it is a relevant database, and it's certainly more population-based than the three percent of patients who participate in clinical trials. However, some approximations about the impact of adjuvant therapy in different groups must be made, because information about them is not included in SEER.

Adjuvant! focuses on the baseline data for untreated patients, and it also incorporates the Overview's data about the efficacy of different adjuvant therapies. The Overview approximates the absolute benefit by multiplying baseline estimates and proportional risk reductions.

One of the strengths of Adjuvant! is its extensive help files which describe the assumptions that underlie some of the estimates. As much as possible, the assumptions in Adjuvant! are based on global composite information, like the Overview.

— Peter Ravdin, MD, PhD

Oncologists, in conjunction with their patients, make decisions regarding adjuvant systemic therapy for primary breast cancer every day. Such decisions need to be individualized based on the characteristics of the primary tumor and the willingness of the patient to undergo toxicities for potential benefits.

When asked about how treatment decisions are made, oncology experts routinely reply that patients need to be informed of the options and that they need to participate in the decision-making process.

The question at hand is: How do physicians best inform themselves and their patients regarding the potential benefits associated with adjuvant systemic therapy for primary breast cancer? In a survey of women who had previously received adjuvant chemotherapy, only a minority of women remembered receiving any estimates regarding their prognosis with or without adjuvant systemic therapy, thus suggesting that there is room for improvement in providing patients with adequate information on adjuvant therapy.

— Loprinzi CL, Thome SD.
J Clin Oncol 2001;19(4):972-9.

Significant advances in the treatment of breast cancer have been made during the last several decades through the conduct of large, prospective, randomized clinical trials. These trials offer clinicians clear estimates of cancer mortality risk and survival benefit with the addition of chemotherapy. However, the wealth of clinical trial data has been accompanied by increasing complexity of decision-making and greater confusion among patients as a result of the myriad options available.

This is especially true for postmenopausal patients with estrogen receptor- and/or progesterone receptor-positive tumors for whom chemotherapy may add marginal extra benefit in addition to hormonal therapy with tamoxifen.

Obtaining accurate information regarding the risks and benefits of all treatment options is an integral part of the patients' decision-making process and subsequent informed consent. In addition, physician influence has been shown to have a great effect on patient preferences for treatment options.

— Chao C et al.
J Clin Oncol 2003;21(23):4299-305.

Ideally, the patient should be given the chance to make the decision about whether to receive adjuvant chemotherapy, using the information oncologists provide. Although some patients will want adjuvant chemotherapy for even a 1% improvement in cure rate, others may find a 5% to 10% absolute improvement in cure rate not worth the short-term side effects of chemotherapy.

However, no matter what the relative benefit of adjuvant chemotherapy is, it behooves oncologists to participate in an honest discussion of the benefits and risks of chemotherapy in every individual patient and give the patient the chance to make the decision for, or against, adjuvant chemotherapy.

— Sonpavde G.
J Clin Oncol 2003;21(5):948-9.

An absolute 1% risk reduction may seem low to some readers, especially when the treatment given is chemotherapy. However, interviews of cancer patients show that a sizable proportion of them (up to one half of them in one study) consider a 1% chance of cure as a valid justification for undertaking chemotherapy.

Patients also would accept a hormone therapy for low expected benefits. Age does not seem to alter the willingness to accept treatment, although older patients may have a somewhat higher threshold in survival benefit to accept the most toxic treatment alternatives.

In the EBCTCG meta-analysis, the absolute decrease in mortality with chemotherapy for node-positive women aged 50 to 69 years was 2.3% at 10 years. Such a well-accepted intervention as beta-blockers after a myocardial infarction leads to an absolute 1.8% decrease in long-term mortality. Similarly, prolonged antiplatelet therapy for various cardiovascular conditions yields a 2% to 5% long-term decrease in mortality.

Therefore, the 1% to 3% absolute reduction in mortality risk that elderly breast cancer patients can expect from chemotherapy according to this model is within the range of effectiveness of common secondary prevention interventions. Given the prevalence of breast cancer in older people, such a degree of benefit translates into a significant impact from a population perspective.

— Extermann M et al.
J Clin Oncol 2000;18(8)1709-17.

FIGURE 10

Actual Cases from Physician Practices

What adjuvant chemotherapy did you use for this patient?

	Node-positive	Node-negative
AC → or + paclitaxel	22%	6%
AC → or + docetaxel	16%	8%
AC	34%	54%
CMF	14%	20%
FEC/FAC	8%	10%
Other	6%	2%

EDITOR'S COMMENT

One of the most surprising findings in this survey was selection of chemotherapy in postmenopausal women with node-positive tumors. In other surveys — including this one — oncologists have claimed that they typically administer a taxane to these patients. However, in this scenario in which the physicians were queried about the last specific patient they evaluated, less than half of the patients received a taxane. This important clue from our pilot effort will now be rigorously evaluated in a more definitive survey with more physicians and greater statistical power.

If the findings hold up, a number of potential explanations could apply, including the perception that taxanes do not provide incremental benefit in women with receptor-positive tumors. Another possible explanation is that based on models like ADJUVANT!, the incremental absolute advantage to taxanes in women already receiving an aromatase inhibitor might not justify utilization. Another surprise was that only about a third of physicians using AC followed by T in these cases delivered therapy with growth factors every two weeks — the dose-dense approach that CALGB-9741 demonstrated to result in an improved survival compared to non-dose-dense AC followed by T.

Related Comments from Research Leaders

We now have a number of adjuvant regimens that are better than the standard regimens. I'm intrigued by the dose-dense approach, but before I adopt it routinely, I want to see confirmation from a second trial. Two trials evaluating AC followed by paclitaxel have reported a significant improvement with that adjuvant regimen.

The NSABP-B-28 trial, which added four cycles of paclitaxel to AC, had results similar to the earlier study. Many oncologists have substituted docetaxel for paclitaxel, and the Taxotere-311 data lends support to that in the adjuvant setting. In a younger patient with node-positive disease who is not eligible for a trial, I am more likely to use AC followed by docetaxel.

The study comparing docetaxel, doxorubicin and cyclophosphamide (TAC) to 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) is a very clean trial.

It is often interpreted as TAC being more effective for patients with one to three positive nodes, but not those with four positive nodes.

That is the way the data were presented, but TAC is pretty effective across the board. Some oncologists have expressed concern about the TAC regimen's toxicity, and it probably requires the use of growth factors.

— Stephen E Jones, MD

I do not use four cycles of AC. I will consider CMF in some patients with node-negative disease who are at low risk. I usually use six-cycle anthracycline-based regimens — typically FEC.

I'm looking forward to the Canadian MA21 trial data directly comparing a six-cycle anthracycline-based regimen to AC followed by paclitaxel. I think this is the "million-dollar question."

Taxanes clearly offer benefits in the adjuvant setting, and I typically utilize the six-cycle TAC regimen. The disease-free and overall survival of dose-dense therapy and TAC are equivalent. Growth factor support, used in conjunction with TAC, reduces the rate of febrile neutropenia to that seen in CALGB-9741.

One of the most interesting questions in adjuvant therapy is: Can a taxane replace an anthracycline? The US Oncology trial presented by Stephen Jones evaluated docetaxel and cyclophosphamide versus doxorubicin/cyclophosphamide. In a population of patients, irrespective of HER2 status, this trial suggests you don't need anthracyclines. The taxanes may really be usurping the role of the anthracyclines.

The BCIRG adjuvant trastuzumab trial also has a novel, nonanthracycline arm — docetaxel/platinum/trastuzumab — in a HER2-positive population. This combination is based on the preclinical in vitro data of synergism with these agents.

— Denise A Yardley, MD

FIGURE 11

Actual Cases from Physician Practices

What side effects did this patient experience?

	Node-positive	Node-negative
Nausea and vomiting	44%	56%
Alopecia	68%	74%
Fatigue	42%	40%
Mucositis	10%	8%
Neuropathy	12%	4%

EDITOR'S COMMENT

Oncologists reported substantial side effects with chemotherapy. In spite of significant advances in prevention of gastrointestinal side effects, about half of these patients experienced nausea and vomiting. It is also possible that physicians underestimate the side effects patients experience.

Related Comments from Research Leaders

As treatment guidelines continue to evolve with newer data, the relative benefits of treatment in many situations continues to grow. …Parallel to this effort, and of equal importance, is the ability to shield patients that will gain little, if any, benefit from treatment and to identify those who may be at greater risk to suffer from potential toxicities. Until these factors are better defined, the recognition by clinicians of long-term side effects associated with adjuvant therapy is obligatory. Acute toxicities from treatment are often reversible, but late onset adverse effects of therapy can increase morbidity and mortality in long-term survivors, and continue to be of concern. One of the most serious side effects of adjuvant therapy of early breast cancer is cardiac toxicity.

— Theodoulou M, Seidman AD. Semin Oncol 2003 30(6):730-9.

The side effects of cancer chemotherapy reported by our patients, along with their ranking by relative severity, formed a distinctive profile. The psychosocial complaint *affects my family or partner* was ranked first as the most severe side effect. Alopecia was ranked second, followed by fatigue (constantly tired). An additional set of psychosocial complaints — *effects on work and home duties, effects on social activities*, and *loss of sexual feeling* — ranked fourth, fifth, and sixth, respectively.

— Carelle N et al. Cancer 2002;95:155-63.

Adjuvant therapy decisions are complicated by marginal differences in treatment results and risk-benefit profiles, balancing acute effects with long-term outcomes. Individual patients differ in the value they place on these issues. Retrospective studies report that women may be willing to undergo treatment for as little as a 1 to 2 percent improvement in the probability of survival. Clear communication of benefits and risks is an essential component in enabling as informed a joint treatment decision as possible. Absolute and relative benefits and risks of therapy must be discussed openly.

— National Institutes of Health Consensus Development Conference Statement November 1-3, 2000

NSABP-B-30 is an important trial because it will answer whether sequential chemotherapy is better than combination chemotherapy in the adjuvant setting. Patients with node-positive breast cancer are randomly assigned to doxorubicin/cyclophosphamide followed by docetaxel versus doxorubicin/docetaxel versus docetaxel/doxorubicin/cyclophosphamide. The rationale for selecting docetaxel is related to the issue of cardiac toxicity. Initial Phase II trials from Europe reported over a 90 percent response rate for paclitaxel when given in combination with doxorubicin. However, an increase in cardiac toxicity was seen when paclitaxel was given in combination with doxorubicin and cyclophosphamide. Although cardiac toxicity may be attenuated by either changing the length of the infusion or by separating paclitaxel from doxorubicin by several hours to a day, these maneuvers may also decrease efficacy.

In Phase II trials, docetaxel did not increase cardiac toxicity when given in combination with doxorubicin. This difference in cardiac toxicity may be related to the different vehicles used to dissolve paclitaxel and docetaxel. Paclitaxel is dissolved in cremophor, which is known to increase doxorubicin's area under the concentration curve (AUC). Docetaxel, on the other hand, is dissolved in polysorbate, which does not increase doxorubicin's AUC.

— Eleftherios P Mamounas, MD

No woman with localized breast cancer can know that she definitely will experience a recurrence in the absence of therapy, and even if she did, there is no guarantee that treatment will prevent such a recurrence. Even women with very early stage disease are at some risk of a systemic recurrence after local therapy alone. The potential benefits of adjuvant treatment need to be considered in conjunction with the risk of short-term and long-term side effects. Not only should the patient and physician consider the frequency and intensity of the side effects, but they must also consider how any particular side effect may impact an individual woman's life.

— Partridge AH et al. J Natl Cancer Inst Monogr 2001;30:135-42.

FIGURE 12

Actual Cases from Physician Practices

What happened during the course of chemotherapy?

	Node-positive	Node-negative
Delay in delivering chemotherapy	14%	14%
Chemotherapy dose reduced during the treatment	0%	2%
Less than planned number of cycles delivered	2%	0%
Febrile neutropenia	6%	6%
Growth factors used	62%	56%
Filgrastim	18%	14%
Pegfilgrastim	36%	32%
Epoetin alpha	20%	16%

EDITOR'S COMMENT

A recent paper by Gary Lyman — based on data obtained in the late 1990s — suggested that breast cancer patients treated with adjuvant chemotherapy in a community setting frequently have the dose reduced, treatment delayed, or less than the planned number of cycles delivered. Based on the self-reporting of our survey, this trend is reversing. Part of this may relate to the extensive use of hematologic growth factors, which were used in more than half of these patients. Note that pegfilgrastim is used about twice as frequently as filgrastim, undoubtedly reflecting the greater convenience of the longer-acting formulation.

Related Comments from Research Leaders

We contracted with over 1,200 non-academic practices of all sizes (but not academic centers) geographically distributed across the country. We asked them to gather information on their last series of patients receiving adjuvant chemotherapy for breast cancer, starting currently and going backward.

These were patients who were treated with a mixture of chemotherapy regimens from the mid-1990s until early 2000. We are just beginning to evaluate patients treated more recently. Our report published in the *Journal of Clinical Oncology* focused on approximately six years of data from approximately 20,000 women. The primary area of interest was dose intensity.

It was a very eye-opening experience. We found that the majority of women underwent some degree of reduced dose intensity from the published reference standards. In fact, 56 percent of women across all regimens are receiving less than 85 percent of targeted dose intensity.

In those patients experiencing dose reductions, approximately 40 percent are planned dose reductions, which I believe reflects an intention to "go light" on the first cycle and then raise the doses for subsequent cycles if the patient tolerates therapy well.

That seldom occurs, even in patients who don't develop neutropenic complications. It's extremely rare for those cycle-specific dose intensities to be raised during subsequent cycles. Once started low, doses continue to remain low. In the unplanned reductions, we believe 60 to 65 percent are due to physician or patient responses to hematologic toxicities and 40 percent are due to non-hematologic complications.

— Gary H Lyman, MD, MPH, FRCP

In breast cancer, we have data from the Budman-Wood CALGB study, which randomly assigned patients to three different relative dose intensities of CAF. This study was published initially in the *New England Journal of Medicine* in 1994 and then in the *Journal of the National Cancer Institute* in 1998 with nine years of follow-up.

A 50 percent reduction in relative dose intensity demonstrated a significant reduction in disease-free and overall survival at five years. The one-third reduction in dose intensity showed a significant decrease in disease-free survival, but overall survival was not yet significantly different.

Why might that be? Can we actually measure the impact of dose intensity and the impact on outcome in patients with a 10 percent, 15 percent, or even 25 percent reduction in relative dose intensity? This is where it becomes very difficult, because it's largely a power issue. Those studies have not been done prospectively.

In 1995, Bonadonna retrospectively evaluated his CMF data and found enormous differences between women who received more than 85 percent of CMF dose intensity on a 28-day schedule versus those who received less than 85 percent.

Patients who received less than 65 percent of standard dose had a disease-free and overall survival no different than that of the control group. The problem with Bonadonna's study is that there are many other potential causes for those reduced dose intensities that might also be related to outcomes.

Retrospective data from the Toronto group and others almost always demonstrated that reducing dose intensity was associated with poorer outcomes, but we really need prospective randomized trials to resolve this issue.

Despite the CALGB trial and a smaller French adjuvant trial — which evaluated FEC 100 versus FEC 50 and showed a significant decrease in disease-free and overall survival with the lower-dose epirubicin — the power calculations would indicate that you literally need thousands of patients in each arm of a trial to measure these kinds of small decrements.

— Gary H Lyman, MD, MPH, FRCP

A retrospective analyses of CMF from Bonadonna in Milan showed that reductions to below 85 percent of planned dose intensity are detrimental to patient outcome, yet there's interesting evidence from Germany and the United States that oncologists lower and delay dose far more often than anticipated.

Several factors cause dose reduction and delays. To begin, the use of growth factors represents a financial and technical barrier. Also, until recently we didn't have convincing data that delaying a few days here and there mattered. In addition, a number of toxicities other than myelosuppression, including fatigue, mucositis, diarrhea and nausea, lead to dose reductions and delays.

Every time we dose-reduce or delay, we may be compromising therapy. Clinicians should ask themselves whether they have evidence that this is safe to do. Right now they don't. All the evidence we have says that dose reductions and delays are not safe.

— Clifford A Hudis, MD

While I rarely use non-dose-dense therapy, for physicians who do and have neutropenic patients on the day of planned therapy, I lean towards the use of growth factors rather than dose-reduction. There is probably a threshold dose important for anthracyclines, and I suspect growth factors are a way of making sure you hit that threshold.

I believe that some physicians "low-ball" patients on the dose of therapy in trying to be "nice" and minimize toxicity.

However, if you start at half the dose because you believe the patient is fragile, you're doing the patient a disservice. I think you need to get the data and treat those patients identically to how they were managed in the protocol.

I think people are becoming more aware that there probably is a threshold effect — the word gets out. I also believe that growth factors allow people to stay on schedule, because you don't see the profound drops in counts and the high rates of neutropenic fever. Hopefully, as we go on, this will translate to better efficacy outcomes in adjuvant therapy.

I'm still not certain why postmenopausal patients in the Overview appeared to receive half the benefit of chemotherapy of younger patients. Biologically, I can't understand why that happens, yet it seems consistent over 15 years in the Overview.

I suspect a large part may be dosing issues in the older studies that dominate the Overview. Perhaps this will change in future analyses.

— Hyman Muss, MD

As previously reported, chemotherapy with CMF, as given in our study [Bonadonna], failed to improve outcome significantly in postmenopausal women, particularly those older than 60 years of age. Many oncologists interpreted these results to mean that the predominant effect of chemotherapy was chemical castration.

We have always maintained that the difference in the effectiveness of the regimen between premenopausal and postmenopausal women was mainly, if not exclusively, due to the low dose of chemotherapy that many postmenopausal patients received, either by protocol design or because of protocol violations, including lack of compliance with the regimen for oral cyclophosphamide.

Our results after 20 years of follow-up confirmed our initial observation. A recent study by the Cancer and Leukemia Group B showed that both premenopausal and postmenopausal women given regimens involving high or moderate doses of cyclophosphamide, doxorubicin, and fluorouracil had significantly better disease-free and overall survival than those given regimens involving low doses.

— Bonadonna G et al. N Engl J Med 1995;332(14):901-6. [Emphasis added, citations omitted]

Dose and dose intensity of administered chemotherapy are clinically important variables that can be manipulated in an attempt to improve DFS and OS in patients with operable breast cancer.

This trial [Budman-Wood Study] examined these parameters within a conventional dosage range. With additional follow-up since our previous report, we are able to confirm that total dose remains a critical determinant of outcome for this group of patients.

Both the moderate-dose and high-dose arms delivered the same cumulative dose of chemotherapy with no significant difference in outcome (DFS or OS) between these arms for the study as a whole, but significantly better survival than for patients treated with a low-dose-intense arm.

The data therefore suggest that dose reduction, perhaps below a threshold, leads to a relatively worse outcome with the currently available drugs for adjuvant treatment of patients with stage II breast cancer.

— Budman DR et al. J Natl Cancer Inst 1998;90:1205-11. [Emphasis added, citations omitted]

FIGURE 13

Dose-Dense Adjuvant Chemotherapy

Have you used dose-dense adjuvant chemotherapy outside a protocol setting?

No	36%
Yes	64%

For those answering "yes," when did you first use it?

1-2 years ago	53%
<6 months ago	47%

For those answering "yes," in about how many patients?

1-10 patients	59%
11-20 patients	28%
>20 patients	13%

FIGURE 14

Choice of G-CSF for Dose-Dense Adjuvant Chemotherapy

When using dose-dense chemotherapy, which growth factor(s) do you use?

Filgrastim	31%
Pegfilgrastim	38%
Both, but mainly filgrastim	3%
Both, but mainly pegfilgrastim	25%
Both about equally	3%

EDITOR'S COMMENT

About two-thirds of oncologists have used dose-dense adjuvant chemotherapy, but recently many have only been using it in a relatively small number of patients.

Although the CALGB-9741 trial utilized filgrastim as part of dose-dense chemotherapy, most oncologists are using the longer-acting formulation, pegfilgrastim, for this purpose.

Related Comments from Research Leaders

CALGB-9741 had a two-by-two factorial design, and the results presented at San Antonio compared the two dose-dense arms to the two sequential arms. One disadvantage of the two-by-two analysis is that it precludes pair-wise comparison of the two dose-dense arms. However, the dose-dense arms had similar findings.

At a median follow-up of three years, dose-dense treatment was associated with a 26 percent proportional reduction in relapse rate and a 31 percent proportional reduction in mortality. We had expected 515 relapses based on CALGB-8541, the CAF dose-intensive trial; however, there were only 315 recurrences.

The four-year disease-free survival was 82 percent for dose-dense therapy and 75 percent for the every three-week regimens.

I was surprised by the magnitude of the difference — seven percent at four years is significant. We'll have to see whether the survival benefit is lost or confirmed with further follow-up.

Most patients received the optimal doses of their drugs in all arms. This assured us that the benefits of dose density could not be attributed to a lower dose or further dose delays in the conventional regimens — the arms were balanced in that regard.

The advantages of dose density were not accompanied by an increase in toxicity. In fact, the major difference in side effects was leukopenia, defined as less than 500 granulocytes, which was significantly more common in the every three-week arms, with a *p*-value of less than 0.0001.

The incidence of hospitalization for febrile neutropenia was also slightly higher in the every three-week arms, but it was uncommon in all arms.

Everyone was concerned about leukemia, but the results do not appear different than the prior protocol, CALGB-9344, at the same exact time point. The incidence is slightly less in the dose-dense arms, although not statistically significant. Dose density also appeared to have no impact on cardiac toxicity, which was less than two percent in all arms.

For certain complications, we had information on only the first 100 patients in each arm. One of these was the incidence of red blood cell transfusions, which was 13 percent on the concur-

rent, dose-dense regimen, while only three percent or less in the other arms.

This is difficult to understand, both from my experience in giving dose-dense therapy and chemotherapy in general, because aggressive use of red-cell stimulating factors generally prevents that complication. This was the only major side effect seen with dose-dense therapy.

Interestingly, severe post-chemotherapy neurologic toxicity was slightly greater in the patients who received concurrent chemotherapy, whether it was every two or every three weeks. I can't explain that, because we don't consider cyclophosphamide to be neurotoxic.

It may be just a statistical quirk, but I've begun asking my patients on AC if they're having any neurological problems. Occasionally I hear complaints of paraesthesias, which I had previously attributed to dexamethasone. I'm watching it more carefully now.

Dose-dense therapy is definitely a therapeutic option for patients with high-risk breast cancer at this time. It is not the standard of care, but rather an alternative to discuss with patients at risk for relapse within the next three or four years.

In my older patients who may not be able to tolerate combination treatment, I use sequential dose-dense ATC, and I think we'll find sequential dose-dense ATC will be tolerated well by the elderly.

I always present patients with their options, and I like to hear what they have to say. In general, patients want the treatment with the most potential for cure. Many also want to receive the treatment quickly — in fact, that's one of the most common reasons patients express for wanting dose-dense therapy.

Most oncologists like to see five years of follow-up in an adjuvant study. I find when I talk to physicians about emerging trends, I can generally divide the reactions into thirds.

One-third embrace it, a second third are not sure and the remaining third are definitely against it.

I've been surprised by how positively dose-dense therapy has been received. As I talk to physicians, I find they are often using or at least considering it. This approach appears to be more widely accepted than I had expected at this time.

— Marc Citron, MD

CALGB-9741 was initially presented by Marc Citron at the 2002 San Antonio Breast Cancer Symposium and subsequently published in the *Journal of Clinical Oncology*. This Intergroup trial with a two-by-two factorial design asked two presumably unrelated questions.

The first question was whether the concurrent administration of AC was better than the sequential administration. The second question was the comparison of every three-week and every two-week therapy. The every two-week therapy was administered with granulocyte-colony stimulating factor (G-CSF) support.

Although CALGB-9741 had four different treatment regimens, it was not a four-arm trial; it was two separate two-arm trials with the same patient population. The trial is easily interpretable because the doses of drugs were the same for all patients in all of the treatment arms.

The planned first analysis was not early or preliminary. At this point, the trial had 90 percent power to detect a one-third reduction in the hazard for either main effect — disease-free or overall survival.

No significant differences were noted between concurrent and sequential therapy; however, dose-dense therapy (ie, every two-week administration) demonstrated a statistically significant improvement in disease-free and overall survival.

We are confident in these results because the hazard function over time for these arms is significant at all points. The every two-week arms are always better than the every three-week arms, with the margin of benefit appearing to widen.

At four years, the risk of recurrence for the every two-week regimen is 50 percent of the risk of recurrence for the every three-week approach. As with any trial, the issue of toxicity is important for CALGB-9741.

Consistent with CALGB-9344 and in an effort to conserve resources, CALGB-9741 collected safety data for all of the patients only in terms of grade III/IV toxicity and severe adverse events. However, detailed blood count and safety data were not collected.

It was believed that if there were no differences in the detailed safety data from 100 patients per arm, then it did not need to be collected from the whole cohort of 2,000 patients. As a result, detailed safety data is available for only about 100 patients per treatment arm.

Patients treated with G-CSF had a profound reduction in the incidence of neutropenia. Febrile neutropenia was reduced by 50 percent, although statistically one can't be sure.

We were surprised by the data on red blood cell transfusions. Of the patients treated with concurrent dose-dense AC and paclitaxel, 13 percent received a red blood cell transfusion, which is difficult to explain, because the incidence of grade III/IV anemia was identical in all four arms of the trial. We do not have data about mild (ie, grade II) anemia.

— Clifford A Hudis, MD

FIGURE 15

Dose-Dense Adjuvant Chemotherapy

When using dose-dense chemotherapy, in what part of the regimen is growth factor support utilized?

Entire regimen	94%
Only in AC part of regimen	6%

Have you used dose-dense AC without a taxane?

Yes	54%

EDITOR'S COMMENT

When CALGB-9741 was first reported in December 2002, there was initial speculation that some oncologists would choose to use weekly paclitaxel without growth factor support in the second part of the regimen instead of the dose-dense every two-week approach. Another speculation was that physicians might attempt to use every two-week paclitaxel without growth factors or "as needed" rather than preventively. As evidenced by this survey, neither of these options seems to be commonly utilized in practice.

Related Comments from Research Leaders

Those of us who have been following the developments in the mathematical model really believe that CALGB-9741 is a positive trial because it addresses this mathematical concept. Others are more skeptical and believe the difference is due to the paclitaxel schedule. We don't have a clear answer.

Ideally, we should evaluate whether the anthracycline or the taxane must be administered in a dose-dense manner. We don't have time to answer these questions, as too many other important questions need to be addressed. However, I believe it's reasonable to use dose-dense AC. In Europe it's not possible to use dose-dense chemotherapy because of financial issues.

— Martine Piccart, MD, PhD

The availability of growth factors and better supportive care measures has enabled us to ask very interesting questions about dose schedule and dose intensity. We have to acknowledge the contributions that Larry Norton and his mathematical models have made in this arena.

CALGB-9741 compared the standard three-week schedule of AC followed by paclitaxel to a dose-dense, every two-week schedule. The study also evaluated a question of sequential monotherapy versus concurrent therapy. The analyses suggested that, while there was no clinically important difference between sequential therapy and concurrent therapy, the every two-week schedule was superior to the every three-week schedule.

If I give sequential AC and paclitaxel, I give it every two weeks instead of every three weeks, because of the survival advantage associated with that regimen. For node-positive patients, I most frequently use dose-dense AC followed by paclitaxel. We feel quite comfortable with this regimen.

— Harold J Burstein, MD, PhD

I believe in dose-dense therapy because I've seen its evolution in the laboratory and the clinic for 25 years, and I believe it has a solid basis. However, no individual can stand up and say this is the new standard of care. We have to see how people are going to utilize this in the community. I would not be shocked to find this approach widely accepted and used, but whether it becomes a new standard of care needs to be defined by the community.

— Larry Norton, MD

As a result of CALGB-9741, the adjuvant trial CALGB-40101 in patients with node-negative disease was amended to use every two-week AC. The proof of greater efficacy with less toxicity was the major consideration in that protocol amendment. In terms of the science, I think it's reasonable to use every two-week AC without a taxane in a nonprotocol setting. I would hypothesize that patients with negative nodes or a low volume of disease may benefit even more.

From years of trials and the worldwide overview pioneered by Richard Peto, we've learned that if something works in patients with node-negative disease, it will work in patients with node-positive disease and vice versa. I don't think it's necessary to show that dose-dense therapy is going to work in patients with node-negative disease.

It is a question of the risk of relapse for the patient. A patient with a six-centimeter, poorly differentiated primary tumor and negative nodes has an enormous risk of relapse, and that patient should benefit as much as a patient with a smaller primary tumor and a few positive nodes.

Aside from any issues of efficacy, the dose-dense approach offers considerable advantages in terms of completing therapy earlier. We offer our patients a choice. We say, "Let's start dose-dense therapy and see how you do. If you really hate it and you need an extra week, we can always delay things." I've not had a single person who wanted a delay. They just want to complete therapy.

— Larry Norton, MD

FIGURE 16

Adjuvant Chemotherapy: Delivering the Planned Dose and Schedule

What percent of your patients receiving adjuvant chemotherapy have the dose reduced by…

More than 15%	7%
More than 30%	2%

What percent of your breast cancer patients receiving adjuvant chemotherapy have a treatment delayed of…

More than one week	11%
More than two weeks	2%

What percent of your breast cancer patients receiving adjuvant chemotherapy do not complete the planned number of cycles?

Incomplete cycles	4%

FIGURE 17

Importance of Delivering Adjuvant Chemotherapy at Full Dose

How important is it to maintain full dose of chemotherapy in these situations? (0 = not important at all, 10 = extremely important)

Patient situation	Adjuvant setting	Percent of MDs rating 10
45-year-old, N2+	9.2 ± 1.1 SD	56%
45-year-old, N-, 2 cm	8.7 ± 1.3 SD	32%
70-year-old, N2+	7.9 ± 1.7 SD	24%
70-year-old, N-, 2 cm	7.1 ± 1.9 SD	14%

EDITOR'S COMMENT

Oncologists seem to be attuned to delivering the planned dose and schedule of adjuvant chemotherapy as evidenced by cases from their practices. When surveyed about their overall use of adjuvant chemotherapy, they report that significant dose reductions or treatment delays are very uncommon, and almost all patients receive the planned number of cycles.

The physicians surveyed were presented with specific patient scenarios related to adjuvant chemotherapy and asked to rank on a zero to 10 analog scale the importance of delivering the planned dose. In these four scenarios, higher scores were given to cases of younger patients at higher risk.

Related Comments from Research Leaders

If changing therapy from every three weeks to every two weeks can reduce the annual odds of death by 31 percent, I shudder to think what going from three to four weeks or from three to five weeks will do in terms of impairing our ability to cure the cancer. Also, with the anthracyclines, the optimal dose seems to be 60 mg/m^2 — higher doses don't provide any benefit, but lower doses rapidly reduce efficacy. I'm worried about both dose modifications and schedule changes.

Reducing doses to avoid toxicities even a little bit gives us, in simulation, a very disappointing result. Cell kill is dramatically impeded by the use of reduced doses of chemotherapeutic drugs.

Consequently, the tumor regrows because the tumor nadir, which may be important for eradication of sublines of tumor cells, is not achieved. To get around dose reductions, the concept of using full doses of drugs sequentially, rather than simultaneously, was hypothesized and tested.

— Larry Norton, MD

Several years ago, data from CALGB-8541 demonstrated that in the adjuvant setting, full-dose conventional-range therapy was significantly better in the treatment of node-positive breast cancer.

The study examined three cohorts of patients, each receiving different doses of CAF, and evaluated the dose delivery and the total cumulative dose.

Patients receiving the higher doses experienced a marked statistical improvement over the observation period in both disease-free and overall survival in all subsets, and that has continued 10 years later.

There was a steep dose-response curve, so we've learned that compromising dose, either initially because of other conditions or reducing dose later, can be detrimental to outcome.

— Daniel R Budman, MD, FACP

FIGURE 18

Nonprotocol Management of Asymptomatic Neutropenia

How do you manage a breast cancer patient who starts AC without prophylactic G-CSF who has an ANC of <300 on the day of treatment?

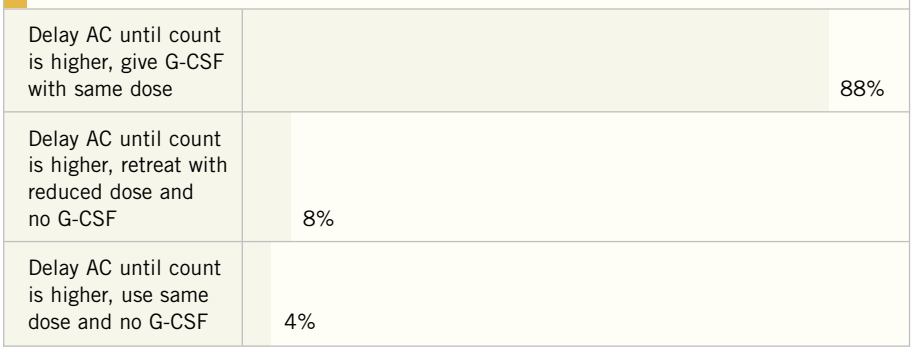
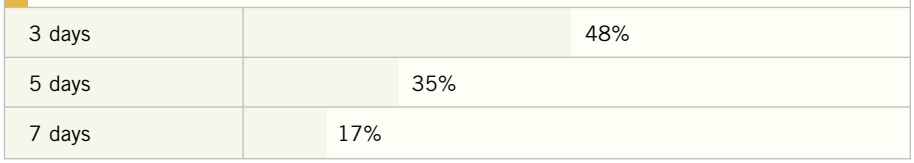


FIGURE 19

Management of Neutropenia after Non-Dose-Dense AC Chemotherapy

When would you repeat the CBC?



EDITOR'S COMMENT

In patients who begin adjuvant chemotherapy without prophylactic growth factor support, neutropenia on the day of treatment is not uncommon. Presented with the scenario of severe neutropenia in this situation, almost all oncologists use the same approach as outlined in most cooperative group clinical protocols — delay treatment until the count recovers, and then include G-CSF with the same dose of chemotherapy.

Related Comments from Research Leaders

Pegfilgrastim is used in the dose-dense arm of the new SWOG-S0221 trial because it certainly makes the regimen more acceptable to patients. Looking at the time course to recovery of neutropenia, it appears that administration every 14 days is possible. Anecdotal results indicate that this is quite tolerable.

Initially, filgrastim will be used in the experimental arm of weekly doxorubicin and daily oral cyclophosphamide. At the University of Washington, pilot studies are being performed to evaluate pegfilgrastim with this regimen. If those studies show that this combination is safe, as expected, then we hope to amend the protocol and use pegfilgrastim in both arms of the study.

— G Thomas Budd, MD

One variable that has changed over time is the use of growth factors. While I can't overemphasize the limitations of retrospective chart reviews, growth factors are not commonly used early in adjuvant therapy of breast cancer like they might be used in patients with lymphomas or those receiving more intensive regimens.

Approximately one-fourth of patients in our study received a hematopoetic growth factor during the course of treatment, but 85 percent received it secondarily after toxicity occurred. Only two to three percent of patients received primary prophylaxis, and those were probably elderly patients or patients with comorbidities.

— Gary H Lyman, MD, MPH, FRCP

The adjuvant chemotherapy regimens for early-stage breast cancer have not demonstrated an extremely high rate of febrile neutropenia. With AC every 21 days, the rates of febrile neutropenia are quite low but somewhat higher with the addition of a taxane. Severe neutropenia — less than 500 neutrophils at the nadir — is probably more common, although I dare say that many of my colleagues aren't even looking at it today because the occurrence of febrile neutropenia is so low.

In 1998, Jeff Silber's group published back-to-back papers in the *Journal of Clinical Oncology*, in which they developed a model based on retrospective analysis of 100 women receiving adjuvant breast cancer chemotherapy.

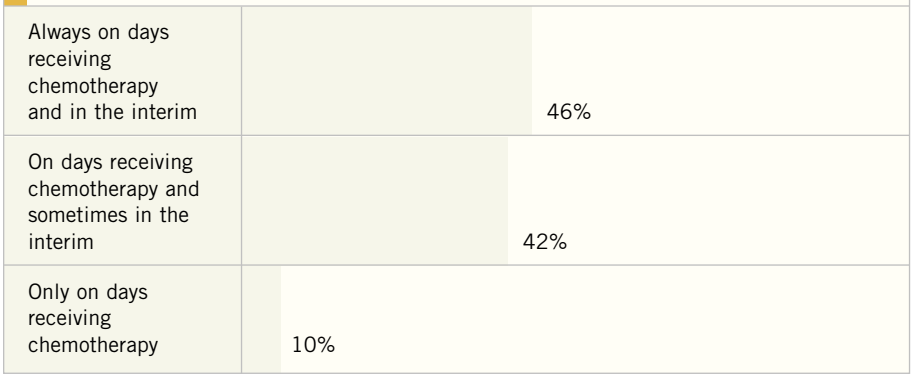
They identified three factors in multivariate analyses that were significant predictors of future dose reductions, treatment delays or neutropenic events that would have led them to reduce dose intensity in those patients. These factors were absolute neutrophil count nadir less than 500 in the first cycle, a drop in hemoglobin from baseline to the midcycle of the first cycle and in patients who had previously undergone radiation therapy.

— Gary H Lyman, MD, MPH, FRCP

FIGURE 20

Nonprotocol Performance of Blood Counts

What is your usual plan for obtaining blood counts for your patients receiving adjuvant chemotherapy?



EDITOR'S COMMENT

Approximately one-half of oncologists routinely obtain blood counts both on the day of chemotherapy and in the interim. Other oncologists are more selective about interim counts.

In the past, patients with neutropenia on the day of chemotherapy administration were asked to return one week later for a repeat blood count. However, with the increasing awareness of trying to deliver treatment as close as possible to the plan, oncologists now more commonly bring patients back three to five days later for a repeat count.

Related Comments from Research Leaders

Managing patients who present with afebrile neutropenia is a challenge. A key issue is the threshold neutrophil count at which one feels comfortable treating. In my career, I've gravitated to using from 800 to 1,000 neutrophils as my cutoff for either delaying or reducing dose.

Typically, I will delay treatment one to three days and repeat counts. I won't delay a full week, which has historically been the "knee-jerk" reaction. Doxorubicin plus cyclophosphamide has a very abbreviated period of neutropenia. It can go quite low, but usually it's not very prolonged, which is probably why these women don't have a very high risk of febrile neutropenia.

In patients with high-risk disease, I do everything possible to avoid reducing their dose. Use of growth factors is an option. Another rational option is to forge ahead with therapy, especially with dose-dense therapy in which we're automatically using growth factor support. I think we're going to find that even women in the 21-day cycles are going to receive growth factors for the future cycles, and they'll probably do fine.

I don't use growth factors universally. I consider age and comorbidities, and if I think chemotherapy presents a real risk of future complications to the woman, I'll add growth factors.

In my experience, probably 25 to 30 percent of patients receive growth factor support at some point. I believe the more rational approach is to target it to the group of patients at the highest risk and do it preemptively as opposed to waiting until they're hospitalized or already neutropenic. Growth factors are much less effective once the patient is neutropenic.

— Gary H Lyman, MD, MPH, FRCP

The current American Society of Clinical Oncology guidelines recommend primary prophylaxis with the CSFs in patients receiving chemotherapy regimens that produce febrile neutropenia in 40% or more of those treated. This recommendation was supported by an early economic analysis based on a decision model incorporating hospital cost data to determine the risk threshold for the cost-saving use of the CSFs.

Updating this model to include current estimates of hospitalization costs, indirect costs such as productivity losses, and out-of-pocket patient expenses reduced the risk threshold for cost savings with CSF to 18%. Recent efforts have focused on identifying individual patient characteristics that might be used to target prophylactic CSF in patients who are at greatest risk.

Should such factors be identified and validated, assessing each patient's individual risk for neutropenic complications may prove to be a better strategy for the cost-effective use of the CSFs than the risk threshold approach.

— Lyman GH. Semin Onc 2003;30(Suppl 13):10-7.

Chemotherapy prolongs survival in patients with early-stage breast cancer, and maintaining the chemotherapy dose intensity is crucial for increasing overall survival. Many patients are, however, treated with less than the standard dose intensity because of neutropenia and its complications. Prophylactic colony-stimulating factor (CSF) reduces the incidence and duration of neutropenia, facilitating the delivery of the planned chemotherapy doses. Targeting CSF to only at-risk patients is cost-effective, and predictive models are being investigated and developed to make it possible for clinicians to identify patients who are at highest risk for neutropenic complications.

— Dang CT et al. Oncology (Huntingt) 2003;17(11 Suppl 11):14-20.

FIGURE 21

Impact of Body Surface Area (BSA) on Chemotherapy Dosing

What chemotherapy regimen would you likely use for a 43-year-old woman who is 5'6" with an ER-negative, HER2-negative, N2+ breast cancer?

Chemotherapy	Dose mg/m^2	
	135 lbs (BSA = 1.7 m^2)	260 lbs (BSA = 2.4 m^2)
AC	10%	10%
AC/paclitaxel	46%	46%
AC/docetaxel	32%	32%

FIGURE 22

Impact of Body Surface Area (BSA) on Chemotherapy Dosing

How would you modify the dose in the heavier woman?

Therapy	No modification	Cap dose at 2m^2	Other
AC	95%	–	5%
AC/paclitaxel	72%	21%	7%
AC/docetaxel	84%	10%	6%

EDITOR'S COMMENT

One of the most challenging questions in adjuvant chemotherapy for early breast cancer is dosing of patients with significant obesity. We presented such a case in our survey, and the regimen selected by most physicians was identical to that selected for the same patient without obesity.

The dosing of the obese patient in our scenario requires further testing in future surveys. Our preliminary findings suggest that most oncologists do not adjust the dose, although a significant minority "round off" to 2.0 m^2.

Related Comments from Research Leaders

We have dosed patients by "per meter squared (m^2)" since the 1960s, but this was based on the erroneous belief that utilizing body surface area (BSA) normalized dosing — the larger the person, the larger the dose. We now know that BSA has very little meaning; the important considerations are how the individual absorbs or metabolizes the drug, and metabolism varies tremendously.

Obese patients raise particular concern. The CALGB examined this issue across adjuvant treatments and recommended we not dose-reduce even the morbidly obese patient. I must admit, most of my morbidly obese patients have comorbid conditions, such as hypertension, diabetes, et cetera, and I am reticent to administer large doses of cytotoxic drugs to such patients. So, despite the CALGB's recommendation, I cap the body surface area at 2.0 m^2.

— Daniel R Budman, MD, FACP

Recent studies suggest that using body surface area to dose drugs like the taxanes may not be optimal. Some institutions are using "flat dosing" for paclitaxel. It may not be any better or worse to use a flat dose of 300 milligrams. BSA may be a poor surrogate for the metabolic rate. Individual variations are far greater than the BSA variations—it's an interesting dilemma.

— Clifford A Hudis, MD

BSA was introduced into medical oncology to safely predict a suitable starting dose in Phase I clinical trials from preclinical animal toxicology data. From that starting point in Phase I trials it has spread throughout the practice of oncology with little justification. The formula to calculate body surface area takes two precisely quantifiable variables, height and weight, and estimates a value for surface area. The formula used to do this has never been adequately validated. Very few of the organ functions that determine the pharmacokinetics of a drug are related to body surface area; further when organ function has been related to body surface area other measures such as lean body weight have been found superior to surface area. For the majority of drugs, the relationship between BSA and kinetics has not been studied and where the relationship between BSA and kinetics has been examined only a few drugs such as the taxanes have relationships been found.

— Sawyer M, Ratain MJ
Invest New Drugs 2001

Every oncologist has a threshold at which they become anxious and begin to adjust weight to ideal, or to some compromise between ideal and actual body weight. In our study, that threshold was extremely variable and particularly dramatic above 2.0 m^2 body surface area. Many practices have patients with BSAs exceeding 2.75 m^2, or even 3.0 m^2, and calculating dose based on actual weight can arouse anxiety. However, for

patients in whom dose was based on actual body weight, there was no greater hematologic toxicity or later dose reduction or treatment delay, at least not in patients with BSAs between 2.0 m^2 and 2.3 m^2.

My oncology group is excited about these findings and about trying to re-evaluate the early data that served as the basis for our approach of dosing based on BSA. In reviewing those early studies, one realizes that a handful of patients were studied with techniques that we could probably improve upon today. We're going back and trying to redo many of the early pharmacokinetic studies to determine if basing dose on BSA — of all the possible options that are out there — still seems to be the most rational approach. It seems to be how most physicians are currently calculating dose.

— Gary H Lyman, MD, MPH, FRCP

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FIGURE 23

Determination of Estrogen Receptor Status

How do you define ER positivity?

Any staining	24%
Staining above lab cut-off	70%
Staining above individual cut-off value you determine	6%

Do you request ER status for ductal carcinoma in situ?

Yes	58%

FIGURE 24

Endocrine Management of DCIS

About what percentage of your patients with DCIS receive tamoxifen?

Mean	62.3%

What percent of your patients started on tamoxifen have difficulty tolerating it?

Mean	16.5%

Have you used an aromatase inhibitor in a patient with DCIS?

Yes	40%

Of those answering "yes," in about how many women?

Mean	9.3

EDITOR'S COMMENT

Pathologist Craig Allred has done a series of important studies that suggest perhaps 20 percent of breast cancer patients are misclassified as having ER-negative tumors. The human and public health impact of this finding is enormous.

Future surveys will further define how oncologists manage this important question. However, most oncologists accept the qualitative diagnosis of the laboratory doing the assay. More than half consider ER results when deciding on whether to use endocrine intervention for women with DCIS — a follow-up to Dr Allred's December 2002 presentation to the San Antonio Breast Cancer Symposium.

Tamoxifen is frequently utilized in women with DCIS, and a substantial fraction of these women have difficulty tolerating it. Surprisingly, more than one-third of oncologists have used an aromatase inhibitor in a patient with DCIS. The NSABP is currently conducting clinical trial B-35, which will randomly assign postmenopausal patients to either tamoxifen or anastrozole.

Related Comments from Research Leaders

European studies have shown that approximately 20 percent of ER assays are false negatives when compared to a reference lab. Estrogen receptor testing is not standardized in the United States or Europe, and this leads to a great deal of suboptimal treatment and misunderstanding of breast cancer biology. For years, we thought that some ER-negative patients responded to hormonal therapy; however, I believe this was merely a result of poor assay methodology.

Part of the problem with these assays is technical, and part is in the interpretation. On the technical side, pathologists are just not used to performing immunohistochemistry. The technique is not standardized. Many pathologists come up with their own methods and only do a few cases a week. This lack of standardization and experience causes technical issues and false-negative results. Interpretation of assay results is a problem in terms of both staining and cutoff values. Many laboratories have established a cutoff that is too high and have labeled tumors with ER as being ER-negative.

We have shown in multiple studies in the advanced-disease, adjuvant and DCIS settings that tumors with more than one percent of cells staining positive are hormone responsive, while tumors with less than one percent of cells staining don't appear to benefit from endocrine therapy.

I believe that medical oncologists often just assume the pathologist is correct. When we started closely reviewing results in our tumor board, it was obvious that there were big problems. Clinicians can insist on having tumors processed in a central laboratory that has a high volume and uses a clinically validated methodology.

— Richard M Elledge, MD

In 1978, the American College of Surgeons conducted a survey demonstrating that 200 out of 24,000 cases of breast cancer were DCIS — less than one percent. The incidence of DCIS exploded in the mammographic era. By screening women, we discovered microcalcifications and other architectural distortions that we otherwise never would have known were present. Some of those women would have developed invasive breast cancer six to 10 years later. Now we intercede in the neoplastic continuum five to 10 years earlier. Today DCIS represents 21 percent of all new cancers.

— Melvin Silverstein, MD

There is variation in defining ER-positivity in Europe and the United States. This variation is extraordinarily disturbing — particularly as our hormonal therapies continue to improve. My feeling is that if there is any receptor present in a tumor, it should be considered positive. Clearly we can miss a very low positive result quite easily, and the result may be that patients who should receive adjuvant endocrine therapy are not receiving it. We need to get this assay correct for every woman.

— Anthony Howell, BSc, MBBS, MSc, FRCP

With minimal training, pathologists in our laboratory were in agreement on discriminating positive from negative tumors in 99 percent of cases. The optimal cut point in our study was a total IHC score of greater than 2, meaning that even patients whose tumors scored 3 (corresponding to as few as one percent to 10 percent weakly positive cells) had a significantly improved response compared to those who had lower scores.

Many hospital and commercial laboratories have converted to assessing ER status exclusively by IHC on archival tissue. They use diverse methodologies, and most have arbitrarily chosen 10 percent or even 20 percent positive tumor cells as their cutoff for defining ER positivity, potentially denying a substantial number of patients the benefits of adjuvant hormone therapy.

— Harvey JM et al. J Clin Oncol 1999;17:1474-81.

Craig Allred presented an abstract at the 2002 San Antonio meeting demonstrating that ER-positive patients in NSABP-B-24 respond well to tamoxifen. The question of whether ER-negative patients respond still seems to be open. ER-negative cases done in Craig's lab showed no apparent effect from tamoxifen.

In NSABP-B-35, DCIS patients will need ER determinations, and only patients with ER-positive or borderline DCIS can take part in the study. We ask for blocks or core samples at headquarters so that we can do ER determinations in a lab like Craig's, and an array of other studies to try to understand more about this disease.

— Richard Margolese, MD

Craig Allred reported very provocative data from the NSABP-B-24 trial on estrogen receptor assays in women with DCIS. A central slide review in the NSABP laboratories found that only women with ER- or PR-positive DCIS derived benefit from tamoxifen in preventing ipsilateral breast tumor recurrence and new contralateral primary tumors. They also found a great deal of disparity in reporting the estrogen receptor data, especially in community centers. Based on this data and Dr Allred's recommendations, it is appropriate to test for estrogen and progesterone receptors in patients with DCIS.

— Hyman Muss, MD

It is clear that DCIS is a highly curable disease from which almost no one should die. If tamoxifen and radiation therapy can reduce the incidence of future invasive cancer to less than two percent, can we achieve even better results?

On the other hand, there are more promising drugs, such as anastrozole. I think it is worthwhile to test anastrozole and see if the small amount of undesired recurrent cancers can be negated. The question becomes: Will anastrozole be any better than tamoxifen, and at what risk?

— Richard Margolese, MD

NSABP-B-35 is the next protocol in a generation of NSABP DCIS trials: B-17 compared radiotherapy to no treatment, B-24 added tamoxifen to lumpectomy and radiotherapy, and B-35, which opened in January 2003, compares anastrozole to tamoxifen for five years. We're hoping that anastrozole will be superior to tamoxifen, as it was in the ATAC trial; however, that trial was powered to detect small differences in efficacy.

We debated considerably whether ER positivity should be required for eligibility in B-35. Dr Craig Allred reanalyzed data from NSABP-B-24 and demonstrated benefit from tamoxifen only in those patients with ER-positive DCIS. Ultimately, we decided to limit eligibility for B-35 to patients with ER-positive DCIS. Only a small subset of women with DCIS — approximately 20 percent — is ER-negative. At the current time, I believe it is overly restrictive and authoritarian to dictate that the community standards require estrogen receptor assay prior to treating DCIS.

— Norman Wolmark, MD

NASBP-B-35 is a large study with 3,000 patients, which will go on for the next five years. It is restricted to postmenopausal patients with DCIS who have ER-positive tumors. Studies in the advanced and adjuvant settings found that anastrozole was at least as good as tamoxifen and perhaps superior. Also, the toxicity was less worrisome — anastrozole doesn't cause uterine cancer or thromboembolism. The issues with anastrozole are that it can't be used in premenopausal women and it may cause osteoporosis, which can be a serious cause of mortality in elderly women.

— Richard Margolese, MD

FIGURE 25

Actual Cases From Practice: Choice of Adjuvant Endocrine Therapy

Which adjuvant endocrine therapy did you use in the last postmenopausal patient you evaluated with an ER-positive breast cancer?

Therapy	Node-positive	Node-negative
Tamoxifen	42%	28%
Anastrozole	50%	60%
Letrozole	6%	10%
Exemestane	2%	2%

FIGURE 26

Choice of Adjuvant Endocrine Therapy and Tumor Size, Nodal Status and HER2 Status

Which endocrine therapy would you likely recommend to a 65-year-old woman with an ER-positive tumor?

Therapy	2.2-cm, N2+ HER2-neg	2.2-cm, N- HER2-neg	0.8-cm, N- HER2-neg	2.2-cm, N10+ HER2-pos
Tamoxifen	34%	33%	43%	23%
Anastrozole	59%	61%	45%	75%
Letrozole	7%	6%	2%	2%
Exemestane	0%	0%	0%	0%

EDITOR'S COMMENT

Based on two recent cases in the practice of the surveyed physicians, the most common adjuvant endocrine therapy being utilized is anastrozole. While letrozole is now often utilized in postmenopausal women completing five years of adjuvant tamoxifen, it is not commonly used up front as an initial adjuvant treatment.

We presented a variety of theoretical scenarios in a 65-year-old woman with an ER-positive tumor and found a correlation between baseline risk of recurrence and use of aromatase inhibitors; however, this needs to be further defined in future surveys.

Related Comments from Research Leaders

The results of the ATAC trial are quite compelling. Even if you assume, for the sake of argument, that the curves will come together with further follow-up, the safety profile of anastrozole is still clearly better than that of tamoxifen. I cannot prevent endometrial cancer short of removing the uterus, but I can prevent or treat osteoporosis and fractures. Because the safety profile of anastrozole is better than that of tamoxifen and it is therapeutically superior, I have a problem not offering anastrozole to my postmenopausal patients — not as a neutral choice, but as a better choice. I discuss with my patients the enormous amount of clinical experience we have with tamoxifen, but I would certainly recommend anastrozole as opposed to tamoxifen.

— Gabriel N Hortobagyi, MD

Initially, I had not changed my clinical practice based on the early ATAC results. I was waiting to see more data and whether or not the curves were coming together. However, at 47 months, the divergence of the curves shows a three percent advantage for anastrozole.

There will not be three-percent events in either arm over the next year; therefore, the anastrozole advantage will continue to be the same or greater in the next year. I will now tell patients that there are two options. One option, tamoxifen, seems less efficacious in the short term, but we know its short- and long-term toxicities.

With anastrozole, the time to relapse is substantially improved at the four-year point, but we really don't have any long-term safety or efficacy data. There is a risk with either therapy, and many patients will want the new therapy with the potential to be better.

— Peter Ravdin, MD, PhD

We have hard data from the ATAC trial, and we will certainly have even more data this summer after another analysis of the data. Virtually all of the patients will have completed therapy for that analysis.

However, so far the absolute difference between tamoxifen and anastrozole, based on four-year data in postmenopausal women with ER-positive, node-negative disease, is about one to two percent. If you use Peter Ravdin's Adjuvant! program, that's the one to two percent of adding chemotherapy.

So, I tell patients the story for chemotherapy is not clear-cut, and it's not clear-cut in patients for whom the benefit is only a few percentage points. Anastrozole may actually accomplish the same thing as tamoxifen and four cycles of AC.

— Gershon Locker, MD

FIGURE 27

Effect of Age on Choice of Adjuvant Endocrine Therapy

Which endocrine therapy would you likely recommend to a woman with a 2.2-cm, ER-positive, HER2-negative, N2+ tumor?

Therapy	55-year-old	65-year-old	77-year-old
Tamoxifen	35%	31%	31%
Anastrozole	60%	63%	64%
Letrozole	5%	6%	5%
Exemestane	0%	0%	0%

FIGURE 28

Use of Adjuvant Aromatase Inhibitors

When you use an aromatase inhibitor as initial adjuvant therapy, what percentage of this use is for each of the following agents?

Anastrozole	84%
Letrozole	14%
Exemestane	2%

EDITOR'S COMMENT

In a baseline node-positive case, no major difference in selection of endocrine therapy was seen related to age, although some research leaders have noted that they are more likely to use anastrozole in older women because of concerns about deep vein thrombosis and stroke.

When asked to recall how often they prescribed specific aromatase inhibitors as initial adjuvant therapy, oncologists most frequently identified anastrozole, reflecting the fact that the ATAC trial is currently the only study with available data in that setting.

Related Comments from Research Leaders

The biggest change in breast cancer has been the advances in hormonal therapy. I was surprised when the early results from the ATAC trial were reported and the benefits with anastrozole were evident so early.

I think the data from the ATAC trial is very convincing. It is a huge trial with more than 9,000 patients, and it is very unlikely that the curves will change over time. However, I am not sure what the long-term toxicities will be. The data already suggests that there may be a higher risk of fracture in women on aromatase inhibitors.

Tamoxifen is generally a safe drug, but women over the age of 70 have an excess risk of stroke. In women over the age of 70, I am compelled to consider an aromatase inhibitor, mostly because of the risk of stroke.

In premenopausal women with multiple positive nodes, I would consider medical oophorectomy. In those types of patients it might be reasonable to use an aromatase inhibitor. In premenopausal women with multiple positive nodes who stop menstruating after chemotherapy and have low estradiol levels, I would also consider an aromatase inhibitor.

— Debu Tripathy, MD

I do not use aromatase inhibitors other than anastrozole in the adjuvant setting because there are no adjuvant data. While we have to extrapolate in a number of situations, I do not see an advantage for the other aromatase inhibitors from the existing data.

It is possible that some time in the future someone will show a distinct advantage to one of these other agents, but at this point, the data were generated with anastrozole, so I use anastrozole.

— Gabriel N Hortobagyi, MD

Counseling postmenopausal patients with regard to adjuvant hormonal therapy requires a lengthy discussion. I refer to studies in the metastatic setting demonstrating a benefit to the aromatase inhibitors over tamoxifen on several endpoints, and I review the ATAC trial results and discuss the risks and benefits of the therapies and the limitations of the data.

Bone density is a big issue for patients. We aim to cure them of their breast cancer, but don't want to leave them with a second problem. I monitor bone density very closely in patients on aromatase inhibitors. I also counsel patients about the side effects of tamoxifen, including endometrial cancer and thromboembolic events, especially those with comorbid conditions and a propensity for clotting.

Over the last six months, I estimate 30 to 40 percent of my patients have chosen tamoxifen and 60 to 70 percent have chosen an aromatase inhibitor. I believe letrozole and anastrozole are probably equivalent, but I typically use anastrozole because the ATAC data is with anastrozole.

With the recent data on tamoxifen followed by the aromatase inhibitors,

this discussion is even more complicated. Some patients are relieved to know some data support changing drugs at the end of five years to give them a little bit more protection.

— Denise A Yardley, MD

In the adjuvant setting I only use anastrozole, because it is the only aromatase inhibitor for which we have data. We can postulate that all three aromatase inhibitors will be active and have similar toxicity, but we don't know that.

In the metastatic setting, letrozole and anastrozole appear to be very similar in both effectiveness and toxicity. Exemestane has not been very well evaluated, but I would wager that the results will be similar.

In the metastatic setting I don't have much of a preference for one aromatase inhibitor versus another. Exemestane may have a superior safety profile in terms of bone, but we should think about its potential steroidal effects.

We need the adjuvant studies with large numbers of patients to address that issue. We're not going to get that answer from the metastatic studies, because there have been too few patients.

— Generosa Grana, MD

Bill Miller and Per Lonning warn us not to make assumptions about the efficacy and tolerability of the three aromatase inhibitors because there are very subtle differences between them. We cannot extrapolate from ATAC to exemestane because there may be differences in efficacy and tolerability between the steroidal and nonsteroidal agents. Exemestane is a permanent antiaromatase with weak androgenic effects.

Letrozole and anastrozole are nonsteroidal aromatase inhibitors, but letrozole appears to produce a slightly greater reduction in aromatase. While one might predict this would cause greater efficacy, the tiny trickle of estrogen left by anastrozole may be important for tolerability. We cannot assume a class effect — we must do the trials.

— Michael Baum, ChM, FRCS

I do not use letrozole for adjuvant therapy in the nonprotocol setting. It's probably equivalent to anastrozole, but I don't see any significant advantages.

If there was a problem with anastrozole, it would have shown up in this study of 9,000 patients, and I would be able to warn my patients or switch them if necessary. With letrozole, I have no way of knowing if there's an issue.

I have been looking at whether exemestane might have some advantages compared to anastrozole. There will be trials to test this. Exemestane is a very different aromatase inhibitor — it's irreversible and it has a steroidal structure. Early laboratory evidence suggests it will not be associated with bone loss.

The resistance mechanisms of exemestane might also be different, which could be better or worse. Remember that tamoxifen can actually be read as an estrogen.

I'm curious to see if a drug with a steroid backbone, such as exemestane, might also be interpreted in some systems as an estrogen. Perhaps the same resistance mechanisms that cause resistance to tamoxifen might also cause resistance to exemestane.

— Peter Ravdin, MD, PhD

As a result of the ATAC trial, my practice pattern changed overnight. I am not treating all of my patients with anastrozole, but I am certainly discussing the results of the ATAC trial and the pros and cons for tamoxifen and anastrozole. I'm using shared decision-making with patients to determine which of the agents they prefer.

Generally, I recommend anastrozole; however, there are other factors to consider which would sway me one way or another. Obviously, in women with an absolute or relative contraindication to tamoxifen, it's a very easy decision. Conversely, there are patients who may have relative contraindications to anastrozole.

The major relative contraindication is severe osteoporosis. The bone mineral density loss associated with the aromatase inhibitors is a concern. Presumably, we can blunt that effect using bisphosphonates, so it is unlikely to be a major problem.

The patient's nodal status does not make a great deal of difference to me in terms of hormonal therapy recommendations. I look at the patient's HER2 status and it shades my thinking a bit. Some data exist, although somewhat contradictory, that HER2-overexpressing tumors may be relatively resistant to tamoxifen.

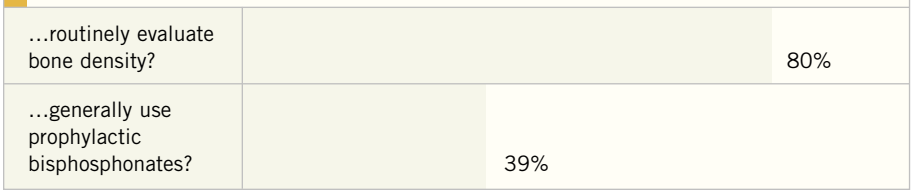
Likewise, data suggest that both letrozole and anastrozole maintain antitumor activity in HER2-overexpressing tumors. I think it would be reasonable to consider anastrozole, in preference to tamoxifen, for patients with tumors that have an IHC score of 2+ or 3+.

— Robert W Carlson, MD

FIGURE 29

Monitoring and Maintaining Bone Density

In your postmenopausal patients receiving adjuvant aromatase inhibitors, do you…



EDITOR'S COMMENT

Most breast cancer research leaders believe that a baseline bone mineral density evaluation is indicated when aromatase inhibitors are started as adjuvant therapy, and that bisphosphonates should not be used for prevention of bone loss in women with normal bone density. Oncologists surveyed do not uniformly follow these procedures.

Related Comments from Research Leaders

The early results of ABCSG-12 demonstrate that the combination of goserelin/anastrozole, and goserelin/tamoxifen to a lesser degree, leads to significant deterioration in bone mineral density in premenopausal women, and that this can be completely counteracted by zoledronic acid.

Even though tamoxifen has an agonistic effect on bone, when combined with the more potent agent goserelin it results in a net reduction in bone density. The bone deterioration is more pronounced with anastrozole/goserelin, but the difference is not significant. The main message is that zoledronic acid was able to completely prevent bone loss, regardless of which hormone combination the patients received.

— Michael Gnant, MD

NSABP-B-34 is evaluating adjuvant clodronate, an oral bisphosphonate, in women with node-negative and node-positive breast cancer. Data from Germany, Canada and the United Kingdom demonstrate that clodronate reduces bone metastases and improves survival. B-34 will randomly assign women to three years of clodronate or placebo. The choice of adjuvant therapy will be left to the investigator's discretion. We chose clodronate because it is the only bisphosphonate with data in the adjuvant setting.

If the B-34 results are positive, hopefully clodronate will be FDA-approved. In lieu of the ATAC trial results, it may be reasonable to combine an aromatase inhibitor with a bisphosphonate as adjuvant therapy.

Eventually, the NSABP plans to compare the bisphosphonates to find the best one. It may, however, be difficult — in terms of patient acceptability — to use an intravenous bisphosphonate in the adjuvant setting.

— Eleftherios P Mamounas, MD

Bone loss can be managed. Dr Gnant presented a study at San Antonio looking at ovarian ablation with anastrozole versus tamoxifen and bisphosphonates. They saw protection from bone loss by adding zoledronate. In addition, the women who received tamoxifen and ovarian suppression without a bisphosphonate had a drop in bone loss, which was corrected when they received zoledronate.

The data presented by Dr Gnant is important with regard to anastrozole because without agents like zoledronate, osteoporosis would be a major issue. This study showed that bisphosphonates have the potential to totally prevent the risk of bone loss.

— Peter Ravdin, MD, PhD

Loss of bone mineral density with anastrozole can be monitored. We don't withhold chemotherapy because we're worried about white cell count — we give it, but we monitor the white cell count.

Osteopenia is not a dramatic crisis like neutropenia. I would check bone mineral density at diagnosis, upon initiation of anastrozole and annually thereafter. I would intervene with a bisphosphonate if it started to fall. The one adverse effect favoring tamoxifen over anastrozole can be managed.

— Michael Baum, ChM, FRCS

The ABCSG trial 12 demonstrated increased bone density from zoledronate at six months and one year among patients treated with an LHRH agonist plus tamoxifen or anastrozole. We need to follow that study because these were early data from only about 100 patients, and it's a much larger trial than that.

I'm regularly asked, "Should I automatically administer a bisphosphonate when starting an aromatase inhibitor?" I would prefer to monitor bone density. There are patients who won't need a bisphosphonate at all. In our update of the MA17 trial of letrozole versus placebo after five years of tamoxifen, we really don't have substantial numbers of fractures.

Currently, there is a one percent fracture rate in the study. Most of our patients aren't going to run into big trouble quickly, so you can do a baseline Dexascan™, monitor patients and institute bisphosphonates at an appropriate time based on the WHO criteria for osteoporosis and osteopenia.

— Julie R Gralow, MD

FIGURE 30

Aromatase Inhibitors with or without Ovarian Suppression in Premenopausal Patients

Have you prescribed aromatase inhibitors in premenopausal women with or without ovarian suppression/ablation (OSA)?

	Adjuvant setting	Metastatic setting
No	66%	49%
Yes, alone	4%	8%
Yes, with OSA	30%	37%
Yes, both alone and with OSA	0%	6%

EDITOR'S COMMENT

Considerable controversy exists about the nonprotocol role of aromatase inhibitors in premenopausal women. While several important ongoing randomized trials are addressing this crucial question in the adjuvant setting, approximately one-third of oncologists are already adapting this strategy into their practices.

Related Comments from Research Leaders

I'm very enthusiastic about the research strategy of evaluating LHRH agonists with aromatase inhibitors. Extrapolating from the data in postmenopausal breast cancer, which suggested that anastrozole may have superior efficacy compared to tamoxifen, this seems like a rational strategy to transfer to premenopausal women. The two issues are whether or not it is actually going to be efficacious, and what the cost is in terms of side effects. I wouldn't utilize this strategy outside the context of a clinical trial.

The adjuvant ovarian suppression trial that I am most enthusiastic about is SOFT — Suppression of Ovarian Function Trial. Premenopausal, ER-positive women who may or may not have received chemotherapy will be randomly assigned to tamoxifen for five years, ovarian suppression/ablation plus tamoxifen, or ovarian suppression/ablation plus an aromatase inhibitor. This very interesting trial will help us address several issues. Does ovarian ablation or suppression add to tamoxifen? And if this is an important strategy, is it better to use tamoxifen or an aromatase inhibitor in women with ovarian suppression?

Two other studies address aromatase inhibitors with ovarian suppression. One is built on the premise — which is pretty popular in Europe — that because we know ovarian suppression is important, some investigators would be unenthusiastic about a trial that didn't involve ovarian suppression. For those investigators, the trial would be ovarian suppression with tamoxifen or ovarian suppression with an aromatase inhibitor.

The other trial asks the question, "If you do ovarian suppression with either tamoxifen or an aromatase inhibitor, do you really need chemotherapy?" This trial randomizes to chemotherapy or not, plus endocrine therapy.

I believe that will be a tough concept to sell in the United States, but it may have some enthusiasts abroad. I think randomized trials that involve two very different treatments, chemotherapy or not, will be a little more difficult to conceptualize.

These trials were put together by the International Breast Cancer Study Group. They have been looked at by the United States cooperative groups, and different groups will decide whether or not to endorse each trial. Subgroups may decide that they are not as enthusiastic about one design or another, and that they want to put all their effort into one. My personal preference is the SOFT trial, because I think it addresses the issues of interest to many United States investigators.

— Nancy Davidson, MD

The IBCSG is coordinating a series of three nested trials: SOFT, PERCHE and TEXT. These trials address what is probably the most important conceptual question in premenopausal breast cancer right now: Beyond tamoxifen, does planned ovarian suppression benefit patients?

In particular, does it benefit women who receive chemotherapy or women who don't receive chemotherapy, and if a woman experiences chemotherapy-related amenorrhea, does she still need ovarian suppression?

We will probably not have the data for at least five or 10 years, but these are very important trials that offer a wonderful opportunity for community oncologists to participate in answering this critical question.

Currently, I consider ovarian suppression for two groups of patients. The first group includes patients at high risk — multiple positive nodes, very high-risk tumors — and particularly young women, less than 35 or 40 years of age, who may not go into menopause with chemotherapy.

The other group includes women who are at the opposite end of the spectrum — very low-risk tumors, smaller tumors, node-negative — for whom the benefits of chemotherapy are very small. I present ovarian suppression as an option for these women, not necessarily in addition to chemotherapy, but perhaps even instead of it.

— Harold J Burstein, MD, PhD

FIGURE 31

Use of Aromatase Inhibitors after Completing Five Years of Tamoxifen

Have you discussed or prescribed an aromatase inhibitor to a woman who has completed five years of adjuvant tamoxifen?

Yes	88%
No	12%

For those answering "yes," in how many patients?

Mean	18

For those answering "yes," which aromatase inhibitors have you prescribed?

Letrozole	92%
Anastrozole	14%
Exemestane	14%

EDITOR'S COMMENT

The Goss paper on post-tamoxifen letrozole had a widespread and immediate impact on practice, and six months later oncologists were uniformly discussing and initiating this therapy. As in the initial adjuvant situation, physicians tend to mirror the source of the research data in choosing an aromatase inhibitor, and letrozole is by far the most common aromatase inhibitor used in this situation.

Related Comments from Research Leaders

Led by the National Cancer Institute of Canada, MA17 randomly assigned over 5,000 postmenopausal women who had received tamoxifen for between four and a half and six years and were free of tumor, to receive letrozole or a placebo.

Letrozole reduced the rate of breast cancer events by about 50 percent, including the risk of distant metastases and the risk of ipsilateral or contralateral breast cancer. The differences were so robust after only two and a half years that the study was closed before completing its planned five-year duration.

The data are exciting because letrozole has the potential to improve the long-term prognosis for the largest demographic group of patients — postmenopausal women with hormone receptor-positive breast cancer. Historically, these women have been offered five years of tamoxifen; now, many such patients should consider taking letrozole after completing that therapy.

It's always exciting to close a study early because of such good news, but follow-up trials are needed to address unanswered questions about the best way to use letrozole in this setting. There are also concerns regarding the profound estrogen deprivation effects of aromatase inhibitors, particularly osteoporosis. We can study those issues, and interventions do exist, but it means we have to pause before blindly recommending this therapy to everyone.

— Harold J Burstein, MD, PhD

On the basis of these findings, postmenopausal women with hormone-receptor-positive tumors who have completed about five years of adjuvant tamoxifen therapy should be considered for letrozole treatment. However, our results, which necessitated the discontinuation of the study, leave the optimal duration of treatment undefined and the question of long-term toxicity unanswered. Data from other, ongoing aromatase-inhibitor trials will contribute information regarding toxic effects, but the question of the optimal duration of treatment will not be answered by the current trials.

Our study did not address the efficacy of letrozole therapy in women in whom tamoxifen therapy had been discontinued more than three months earlier, but because there was an ongoing reduction in the hazard of recurrence in the letrozole group, the use of the drug in such women should be considered. Consequently, our trial committee has recommended that women in the placebo group in our study discuss their personal risk profile with their oncologist and be considered for letrozole therapy.

— Goss PE et al.
N Engl J Med 2003;349(19):1793-802.

The dramatic results from the NCIC-CAN-MA17 trial of letrozole after tamoxifen have thrown everyone into turmoil. The levels of significance are so great that neither physicians nor patients can ignore them. However, we don't have survival data, and it will be difficult to evaluate survival at any point in the future. Additionally, we won't be able to replicate those results because it wouldn't be ethical to repeat that study.

It may be reasonable to offer an aromatase inhibitor to patients who completed a five-year course of adjuvant tamoxifen for as long as five or 10 years previously. However, with every year that passes, the absolute risk of recurrence decreases; therefore, the risk-to-benefit ratio changes. Every year the risks become more important relative to the benefit. As the risk of recurrence decreases, the toxicities of therapy become much more important.

— I Craig Henderson, MD

FIGURE 32

Actual Case: Last Postmenopausal Patient Evaluated Who Has Recently Completed Five Years of Adjuvant Tamoxifen

Median age: 65

Originally node-positive	29%

Mean number of nodes for node-positive patients = 2

Other significant medical conditions	18%
Problems with tamoxifen	56%
Vasomotor symptoms	48%

FIGURE 33

Actual Case: Last Patient Evaluated Who Has Recently Completed Five Years of Adjuvant Tamoxifen

What treatment plan did you use?

Observation	40%
Anastrozole	3%
Letrozole	57%
Exemestane	0%

EDITOR'S COMMENT

When asked to describe the last postmenopausal woman in their practice who was evaluated after completing five years of adjuvant tamoxifen, a profile emerged of a woman with a node-negative tumor who had significant problems with vasomotor symptoms from tamoxifen.

More than half of these patients were started on letrozole. It will be interesting in future surveys to identify factors associated with prescribing letrozole versus observation in these patients.

Related Comments by Research Leaders

The risk reduction seen in MA17 included both distant metastases and second breast cancer events — either in-breast recurrence or secondary contralateral breast cancers. These local regional recurrences constituted a relatively large fraction of all the breast cancer events seen in MA17. For most women who have had one breast cancer event, their greatest threat to survival is the breast cancer we already know about, rather than a second breast cancer event. For the well-informed patient, the data can be interpreted to offer a secondary benefit — chemoprevention.

The use of aromatase inhibitors in prevention is being explored by a number of investigators. The differences in the ATAC trial are relatively modest, but a trend remains favoring the aromatase inhibitor in terms of preventing second in-breast recurrences or contralateral breast cancers. It suggests that two things are going on — continued control of microscopic distant metastases and ongoing improvement in reducing the risk of primary breast cancer.

—Harold J Burstein, MD, PhD

We don't know for how long after a patient completes five years of adjuvant tamoxifen it is still beneficial to initiate letrozole. I consider the data from the NSABP-P-1 prevention trial and the patient's risk to guide me. The P-1 trial showed that if we intervene, we change a woman's hazard rate for breast cancer occurrence, but we don't know at what point the reduction in hazard rate becomes so low it is of marginal value.

For a patient with a 1.1-centimeter, node-negative breast tumor, intervention might still be beneficial a couple years after they finish tamoxifen, but for a patient with eight positive nodes and a 2.5-centimeter tumor, I would be willing to treat them further out because the hazard rate is probably still relatively high. When the results of the MA17 trial were revealed, the patients on placebo were offered letrozole even though we didn't know whether it would be effective two or three years after tamoxifen.

— Clifford A Hudis, MD

All patients with Stage II or Stage III disease who have recently completed a five-year course of adjuvant tamoxifen should receive an aromatase inhibitor. Whether patients with Stage I disease should receive an aromatase inhibitor is an open question because they have a relatively small amount of residual risk. The aromatase inhibitors can be quite expensive for a fairly marginal benefit in patients with very low-risk disease. Additional costs are associated with monitoring bone mineral density or treating with a bisphosphonate. I would like to see more data in Stage I patients.

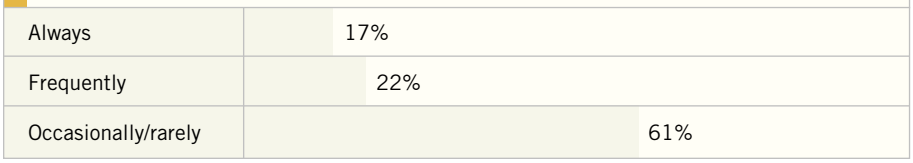
— Peter Ravdin, MD, PhD

FIGURE 34

Use of Aromatase Inhibitors after Completing Two to Three Years of Tamoxifen

Are you discussing switching to an aromatase inhibitor in such patients?

For those answering "yes," with what frequency?



EDITOR'S COMMENT

Discussions about switching to aromatase inhibitors occur less frequently with women who have received two to three years of tamoxifen, but almost one-half of oncologists have had these discussions with patients.

Related Comments by Research Leaders

I am usually conservative, especially with my work. This is a relatively small trial and the data are still early, so we need to be cautious and avoid over-interpretation of it. However, that being said, the data speaks for itself and supports an advantage for switching to anastrozole following two to three years of adjuvant tamoxifen. This data also fits in with previous data from a prior study with aminoglutethimide, the ATAC trial and MA17, all pointing in the same direction.

While I do not believe we have the level of evidence necessary to change our guidelines, in my opinion it is reasonable to switch a subset of women from tamoxifen to an aromatase inhibitor after two, three or five years of therapy. There is no reason today to continue tamoxifen in a woman who might be at risk with this drug, because we now have an alternative.

— Francesco Boccardo, MD

Our large, multicenter study challenges the concept of five years of monotherapy with endocrine agents after the surgical treatment of primary breast cancer. Two smaller studies conducted by Italian researchers have used sequential aminoglutethimide after tamoxifen therapy in 308 patients and anastrozole after tamoxifen therapy in 426 patients. Although they were underpowered, both trials suggested that the sequence may be better than tamoxifen alone, supporting the results we present here….

Our results add to the evidence that the sequential use of aromatase inactivators and tamoxifen provides additional options for improving adjuvant endocrine therapy for postmenopausal women with hormone-responsive primary breast cancer. Our results indicate that five years of tamoxifen monotherapy after surgery may be suboptimal for postmenopausal patients with estrogen-receptor-positive breast cancer and suggest that clinicians should consider switching patients to exemestane between two and three years after the start of tamoxifen therapy.

— Coombs C et al. New Eng J Med 2004;350(4):1081-92.

I don't feel compelled to switch patients to an aromatase inhibitor after just two years of adjuvant tamoxifen. While the switching trials demonstrate the value of adjuvant aromatase inhibitors, we don't know the ideal time to integrate them. It might be just as good, or better, to wait five years and then switch to letrozole.

On the other hand, with patients just finishing five years of adjuvant tamoxifen, I always discuss the results of MA17. The difference is that switching after just two or three years means trading a proven standard therapy for a therapy that may or may not be superior. After five years of tamoxifen the standard has been to discontinue therapy, but based on the MA17 data, switching to letrozole, which has a demonstrated improvement in disease-free survival, seems reasonable.

— Clifford A Hudis, MD

In an article published in the *Journal of Clinical Oncology* in 1996, Dr Saphner et al, reviewing trials from the ECOG database, evaluated the annual hazard rates of recurrence for breast cancer after primary therapy. Patients with four or more positive nodes had a higher risk of recurrence in all time intervals. I believe nodal involvement is key to the risk of recurrence after the first five years.

Letrozole is appropriate in a patient with node-positive breast cancer who completed five years of tamoxifen a year or two ago, but if four or five years have passed and the patient had a small tumor and node-negative disease, the benefit of letrozole would be marginal.

One issue raised by the MA17 and ATAC trials is the selection of endpoints in adjuvant studies. In looking at recurrences, these trials included contralateral, local and regional recurrences. In the future, I suspect we'll be more interested in the distant disease recurrence endpoint. If we had used that as the endpoint in the MA17 trial, the study would probably still be open and we may have obtained additional information.

— Nicholas J Robert, MD

FIGURE 35

Actual Case: Last Postmenopausal Patient Evaluated Who Has Completed One to Three Years of Adjuvant Tamoxifen

Median age: 63

Originally node-positive	24%

Mean number of nodes in node-positive tumors = 2

Other significant medical conditions	16%
Problems with tamoxifen	66%
Vasomotor symptoms	56%
Vaginal/gynecologic	12%
Weight gain	18%

FIGURE 36

Actual Case: Last Postmenopausal Patient Evaluated Who Has Completed One to Three Years of Adjuvant Tamoxifen

What treatment plan did you use?

Continue tamoxifen	88%
Switch to an aromatase inhibitor	12%

EDITOR'S COMMENT

When asked to describe the most recently treated postmenopausal woman in their practice who was on adjuvant tamoxifen for one to three years, the profile emerged of a woman in her sixties who is having problems with vasomotor symptoms — similar to the profile of the patient after five years of tamoxifen as previously mentioned.

At the time of the survey, oncologists did not frequently switch patients in their first five years of tamoxifen to an aromatase inhibitor.

Related Comments by Research Leaders

Over the past couple of decades, tamoxifen has had a huge impact on the management of breast cancer, but its use in the adjuvant setting may be declining. Several studies have demonstrated the superiority of aromatase inhibitors over tamoxifen, including the ATAC trial, the NCIC-CAN-MA17 trial in which women received letrozole after five years of tamoxifen and two trials in which women were switched to an aromatase inhibitor after two or three years of tamoxifen. The Intergroup study, utilizing exemestane, and Boccardo's trial, utilizing anastrozole in node-positive breast cancer, demonstrated an advantage to switching early from tamoxifen to the aromatase inhibitor.

When I use endocrine therapy in newly diagnosed patients, I select anastrozole. If I'm going to switch therapy after two or three years of tamoxifen, I use exemestane, but after five years of tamoxifen, I choose letrozole.

— Nicholas J Robert, MD

SELECT PUBLICATIONS

Allred D et al. **Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: findings from NSABP Protocol B-24.** *Breast Cancer Res Treat* 2002;**Abstract 30**.

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

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

Boccardo F et al. **Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: results of an Italian cooperative study.** *J Clin Oncol* 2001;19(22):4209-15. **Abstract**

Coombes RC et al. **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**

Delozier T et al. **Delayed adjuvant tamoxifen: ten-year results of a collaborative randomized controlled trial in early breast cancer (TAM-02 trial).** *Ann Oncol* 2000;11(5):515-9. **Abstract**

Distler W et al. **Impact of age on the gynecologic adverse event (AE) profile of anastrozole (A) or tamoxifen (T) in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2004;Abstract 770. **Abstract**

Dowsett M et al. **Analysis of time to recurrence in the ATAC (Arimidex, tamoxifen, alone or in combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;**Abstract 4**.

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

Harvey JM et al. **Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer.** *J Clin Oncol* 1999;17(5):1474-81. **Abstract**

Howell A et al. **Effect of anastrozole on bone mineral density: 2-year results of the Arimidex (anastrozole), tamoxifen, alone or in combination (ATAC) trial.** *Breast Cancer Res Treat* 2003;Abstract 129. **Abstract**

FIGURE 37

Use of Adjuvant Taxanes

When you utilize a taxane in the adjuvant setting, which one do you generally use?

Paclitaxel	40%
Docetaxel	58%
Both equally	2%

Have you used adjuvant taxanes in patients with node-negative tumors?

Yes	74%

For those answering "yes," in about what fraction of patients with node-negative tumors do you use taxanes?

Mean	26%

EDITOR'S COMMENT

Docetaxel is being utilized somewhat more frequently than paclitaxel in the adjuvant setting. Most physicians have prescribed a taxane in the therapy of a node-negative patient, but only in a minority of patients — most likely those at higher risk.

Related Comments from Research Leaders

Adjuvant AC followed by docetaxel is being used by many oncologists in practice, but we don't know how it compares to dose-dense AC followed by paclitaxel. Indirect evidence suggests that docetaxel is better than paclitaxel. A direct comparison between paclitaxel and docetaxel administered every three weeks in patients with metastatic breast cancer, presented at the 2003 San Antonio Breast Cancer Symposium, demonstrated a survival advantage for docetaxel.

The data from the randomized Intergroup adjuvant trial will be reported in the next 18 to 24 months, and I will wait to draw a final conclusion at that time. In that trial, which is closed to accrual, patients were randomly assigned to either paclitaxel or docetaxel and to either an every three-week regimen or a weekly regimen. I believe paclitaxel may be better when administered weekly, and docetaxel may be better when administered every three weeks. It will be interesting to see how weekly paclitaxel will compare to every three-week docetaxel.

— I Craig Henderson, MD

At ASCO 2003, I presented the first planned analysis of an adjuvant trial comparing four cycles of docetaxel and cyclophosphamide (TC) to four cycles of doxorubicin and cyclophosphamide (AC). The trial was underpowered with a total of 1,016 patients and approximately 500 patients per treatment arm.

The patients were pre- or postmenopausal and had either node-negative or node-positive disease. At 42 months of follow-up, there were fewer recurrences in the patients treated with TC than those treated with AC.

We had previously demonstrated that TC was somewhat better tolerated than standard AC. Patients treated with TC had some of the usual docetaxel-related side effects (eg, arthralgias, peripheral neuropathy), but they had less mucositis, anemia, nausea and vomiting.

I use adjuvant TC for patients as an alternative to anthracycline-based regimens and I've used TC in patients with heart disease or those previously treated with doxorubicin. I see little reason to use CMF. The TC regimen has no cardiac toxicity or long-term toxicities at 42 months.

For many patients with node-negative disease, four cycles of adjuvant AC is standard treatment, but if there were any hesitancy to use it because of heart disease or other issues, I would use four cycles of TC.

— Stephen E Jones, MD

When NSABP-B-30 was designed in 1997, taxanes were not routinely used in the adjuvant setting. Many of the investigators, including myself, believed that docetaxel was the most active agent in metastatic disease, and that it should be investigated in the adjuvant setting, which is why we included it in all three arms of B-30.

We also wanted to compare the various durations of treatment, so while the AC followed by docetaxel arm is a six-month treatment, the other arms are shorter in duration.

The NSABP data showed four cycles of AC was effective, and we felt that four cycles of AT or TAC would also be effective. Perhaps with hindsight, based on the TAC data, it would have been better to go with six cycles of TAC, but no data show six cycles are superior to four.

Early in the study we had several deaths in the ATC arm of B-30, probably due to the doses used — doxorubicin 60 mg/m^2, docetaxel 60 mg/m^2 and cyclophosphamide 600 mg/m^2. We changed the doses to those used in Nabholtz's regimen — doxorubicin 50 mg/m^2,

docetaxel 75 mg/m^2, and cyclophosphamide 500 mg/m^2 — and since then we've had very few deaths.

We also changed the AT arm from doxorubicin 60 mg/m^2 and docetaxel 60 mg/m^2 to 50 mg/m^2 and 75 mg/m^2, respectively. The TAC regimen produced a high rate of febrile neutropenia — about 29 percent in the metastatic setting and 23 to 24 percent in the adjuvant trial — which we felt was unacceptable, so we added growth factors. It is up to the investigators whether they use the long- or shorter-acting growth factor.

— Sandra Swain, MD

Several clinical trials have addressed the benefit of taxanes in the adjuvant setting. The results from CALGB-9344 have been published and demonstrate an improvement in disease-free and overall survival with the addition of paclitaxel to AC chemotherapy. BCIRG-001 — comparing TAC to FAC — also resulted in an improvement in disease-free survival. Most recently, CALGB-9741 documented an improvement in disease-free and overall survival with dose-dense AC and paclitaxel every two weeks with growth factor support.

Some physicians dismiss the findings from CALGB-9741, believing there is minimal clinical application of the results. I disagree. Increasing the frequency of administration of AC and paclitaxel from every three weeks to every two weeks, with filgrastim support, clearly resulted in a substantial improvement in disease-free survival.

Interpretation of the results is controversial because CALGB-9741 was designed before the administration of weekly taxanes. Today, studies such as the Intergroup's ECOG-N9831 — for patients with node-positive, HER2-positive disease — use weekly paclitaxel. We've seen a shift in the administration schedule of paclitaxel, and some physicians question whether the improvement in disease-free survival was due to increasing the density of paclitaxel, AC or both. That issue remains unresolved, but a dose-dense approach is an acceptable option for women with node-positive early breast cancer.

— Vicente Valero, MD

The management of patients with node-positive breast cancer has become more complex in the last year, and we now have several very good regimens. However, we don't have proof that any of these regimens is absolutely better than another. The options today include the FEC regimen, which is not commonly used in the United States, the TAC regimen and sequential AC followed by paclitaxel or docetaxel.

If I'm going to use AC followed by a taxane, I tend to use the dose-dense regimen published in the *Journal of Clinical Oncology* based on CALGB-9741, or I may still use AC once every three weeks followed by weekly paclitaxel.

If I were to use docetaxel, then I would use AC once every three weeks followed by docetaxel once every three weeks, because of docetaxel's tolerability when administered once every three weeks compared to weekly. When I use the AC every two-week regimen, I use pegfilgrastim rather than filgrastim. While we do not have data on that, I believe it is much more convenient for patients, and we have incorporated it into our clinical practice.

— Edith Perez, MD

In SWOG-S0221, the combination dose-dense arm of CALGB-9741 was selected for the initial randomization instead of the sequential arm. Our rationale was to shorten the duration of treatment and to make it more comparable to the AC regimen in the experimental arm.

In the second randomization, we were originally going to compare docetaxel alone to docetaxel plus capecitabine. We decided to compare paclitaxel every two weeks to paclitaxel every week for a couple of reasons. First, the docetaxel/capecitabine combination is being investigated in several other multicenter adjuvant trials.

Second, it was felt that we should preserve the control arm from CALGB-9741, which administered paclitaxel every two weeks. At the end of SWOG-S0221, we hope we will know the optimal way to administer paclitaxel in the adjuvant setting.

— G Thomas Budd, MD

As a first- or second-line chemotherapy in patients with advanced breast cancer, Taxotere has significant antitumor activity, with response rates ranging from 44% to 68%. This impressive single-agent activity is better than that observed in historical control phase II trials of single-agent Adriamycin and is similar to the results obtained with the standard combination chemotherapy regimens including cyclophosphamide/Adriamycin/fluorouracil (CAF); cyclophosphamide/methotrexate/5-flouruouracil (CMF); and Adriamycin/cyclophosphamide (AC).

Importantly, studies involving Taxotere from the University of Texas at San Antonio, EORTC, and MD Anderson document the highest response rates yet observed in patients with anthracycline-resistant advanced breast cancer. This apparent non-cross-resistance suggests that a combination of Adriamycin plus Taxotere may be advantageous.

— NSABP-B-30 protocol, Rationale, November 14, 2002 [Citations omitted]

FIGURE 38

Use of Adjuvant Taxanes

What is the most common adjuvant chemotherapy regimen you utilize in women with node-positive tumors?

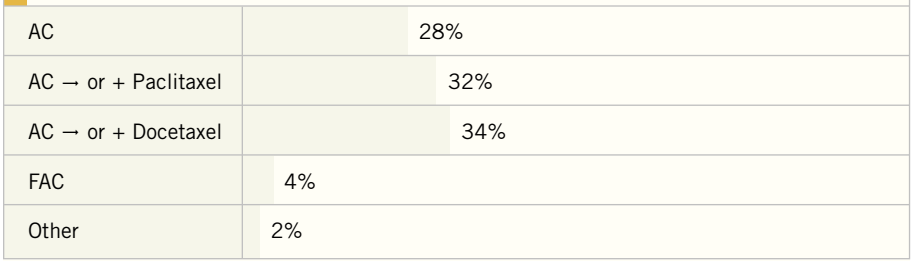


FIGURE 39

Use of Adjuvant Taxanes, Doxorubicin and Cyclophosphamide

When you use these three agents in the adjuvant setting, do you generally use…

EDITOR'S COMMENT

About two-thirds of physicians state that they generally use taxanes in node-positive cases. This contrasts to the actual case they described from their practice (see page 11, Figure 10) of a woman with an ER-positive, node-positive tumor, for whom the most common regimen used was AC.

TAC is the most common regimen used when taxanes are combined with AC, but AC followed by a taxane is by far the most frequent approach to delivering these agents.

Related Comments from Research Leaders

Two trials evaluating AC followed by paclitaxel have reported a significant improvement with that adjuvant regimen. The NSABP-B-28 trial, which added four cycles of paclitaxel to AC, had results similar to the earlier study. Many oncologists have substituted docetaxel for paclitaxel, and the Taxotere-311 data lend support to that in the adjuvant setting. In a younger patient with node-positive disease who is not eligible for a trial, I am more likely use AC followed by docetaxel.

The study comparing docetaxel, doxorubicin and cyclophosphamide (TAC) to 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) is a very clean trial. It is often interpreted as TAC being more effective for patients with one to three positive nodes, but not those with four positive nodes. However, that is the way the data were presented, and TAC is pretty effective across the board. Some oncologists have expressed concern about the TAC regimen's toxicity, and it probably requires the use of growth factors.

— Stephen E Jones, MD

We're participating in the Intergroup trial CALGB-40101, led by Larry Shulman, which asks, "Is AC for six cycles better than four cycles?" This study also attempts to determine whether anthracyclines are necessary or whether they could be replaced with a taxane to avoid the cardiotoxicity. It's a four-arm study — AC for four cycles or six cycles every two weeks, or paclitaxel administered every two weeks for four versus six cycles. After the dose-density data were presented they decreased the timing from every three weeks to every two weeks, all with growth factor support.

— Julie R Gralow, MD

The TAC data were not surprising; I expected them to become positive for survival and disease-free survival. The analysis was very clear — no question — TAC is better than FAC. Now the question is: Is the dose-dense regimen, presented by Marc Citron last year, of AC every two weeks for four cycles with growth factors, followed by dose-dense paclitaxel for four cycles, better or worse than TAC?

The trial comparing TAC to FAC utilized an intravenous FAC regimen, but we've known for a long time that the SWOG FAC regimen is probably better. SWOG FAC uses daily oral cyclophosphamide, which prolongs its administration compared to the all-intravenous regimen.

As established by randomized trials, classic CMF using oral cyclophosphamide is superior to an all-intravenous CMF regimen. Therefore it's even more plausible that classic FAC would be better than the all-intravenous FAC regimen. Although TAC is better than intravenous FAC, it cannot be concluded that TAC is better than the SWOG FAC regimen.

— I Craig Henderson, MD

FIGURE 40

Use of Taxanes in Metastatic Disease

What treatment would you generally prescribe to a woman treated two years ago with adjuvant AC for an ER-negative, HER2-negative tumor who now has rising tumor markers and asymptomatic bone metastases?

	First-line		Second-line	
Therapy	Age 57	Age 75	Age 57	Age 75
Docetaxel	52%	40%	20%	28%
Paclitaxel	17%	4%	12%	20%
Capecitabine	19%	40%	28%	26%
Vinorelbine	4%	12%	16%	20%
Other	8%	4%	24%	6%

FIGURE 41

Use of Taxanes in Metastatic Disease

What treatment would you generally prescribe to a woman treated two years ago with adjuvant AC for an ER-negative, HER2-negative tumor who now has bone and lung metastases and is very symptomatic?

	First-line		Second-line	
Therapy	Age 57	Age 75	Age 57	Age 75
Docetaxel	27%	46%	4%	6%
Docetaxel/capecitabine	38%	18%	2%	4%
Paclitaxel	10%	16%	6%	6%
Capecitabine	13%	8%	24%	30%
Vinorelbine	–	6%	32%	22%
Gemcitabine	0%	0%	16%	14%
Other	12%	6%	16%	18%

EDITOR'S COMMENT

Most women receiving first-line treatment for metastatic disease have had prior adjuvant therapy, and many have at least had AC. Docetaxel is the most common single agent utilized when a patient has previously had AC. Paclitaxel and capecitabine are also frequently selected in this situation. For older women, capecitabine is much more frequently used.

While the strategy of using sequential single-agent chemotherapy is standard in patients who are clinically stable, combination therapy is used by many oncologists in patients with poor performance status. This trend is far less evident in older women.

Related Comments from Research Leaders

The results of the Taxotere-311 trial were surprising, and I didn't think they would be quite so dramatic. For the evaluable patients, a significant difference was seen in the response rate, time to tumor progression and survival in favor of docetaxel. More toxicity was associated with docetaxel than with paclitaxel, but it was the usual manageable toxicity.

This study basically confirmed that docetaxel was probably a more potent taxane, at least on an every three-week schedule. The survival advantage was surprising because few regimens have a documented survival advantage in patients with metastatic breast cancer.

— Stephen E Jones, MD

Combination versus single-agent chemotherapy in the metastatic setting is currently a big debate in oncology. I use combinations in some patients and single agents in others, and I believe the heterogeneity of the disease warrants that. Dr Sledge's trial demonstrated the response rate and the time to progression were significantly in favor of the combination regimen, but overall survival was equal to that of single agents with the crossover.

I may consider using a combination regimen to control the disease more quickly in very young patients, those with a very short disease-free interval, visceral disease or a large tumor burden. In the chemotherapy-naïve patient, I typically incorporate a taxane up front either as a single agent or in combination — often with a platinum.

Sequencing of single agents in the metastatic setting is basically a patient-physician decision. I evaluate prior adjuvant therapy, the disease location, the patient's last regimen, quality-of-life issues and side-effect profiles. I don't believe we have data suggesting a certain sequence to which one should adhere.

The drug that's given earliest tends to have the highest response rate, and it drops sequentially thereafter.

— Denise A Yardley, MD

George Sledge's Phase III trial of single-agent doxorubicin, paclitaxel versus the combination of doxorubicin/paclitaxel as front-line chemotherapy for metastatic breast cancer failed to show a survival benefit for the combination. It's difficult to demonstrate a survival advantage in front-line metastatic disease because, according to the MD Anderson series, these patients live an average of four years.

What you do early in their treatment may never be reflected in a survival advantage because they have many other opportunities for treatment down the line.

In chemotherapy-naïve patients with metastatic disease, I generally use capecitabine/docetaxel (XT). There's no evidence that administering an anthracycline after a taxane harms the patient in any way. I eventually use an anthracycline; I just don't feel compelled to use it up front.

The decision to use single-agent taxane or single-agent capecitabine or the combination for frontline therapy depends on factors such as the patient's presentation and the extent of her disease.

As we begin later-line therapy, when patients become more symptomatic and heavily tumor-burdened, and their life expectancy is shortening, a very reasonable argument can be made for better palliation and maybe even better survival with a well-tolerated combination regimen.

— Joyce O'Shaughnessy, MD

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

Regarding toxicity, the best agents are probably capecitabine and vinorelbine. Alopecia is often an issue for women, and capecitabine is not associated with hair loss. If one is careful with the capecitabine dose, most side effects can be avoided. Over time, some women may experience chronic changes in their hands and feet, but that is the predominant toxicity encountered with capecitabine.

In addition, I find when it's time for a patient to switch from hormonal therapy to chemotherapy, switching to capecitabine is not such a big step for them psychologically.

— Eric P Winer, MD

ECOG-1193 compared doxorubicin followed by paclitaxel, paclitaxel followed by doxorubicin, and the combination of the two agents at initial relapse. The overall response rate for the combination of agents was better than that of either single agent. The time to treatment failure was approximately two months longer for the combination than for either single agent, but overall survival and quality of life were identical among the three arms.

My personal bias is this data provided support for the use of sequential single-agent chemotherapy. In my clinic, I find single agents to be less toxic in many cases, and I frequently offer patients with metastatic disease single-agent chemotherapy.

Joyce O'Shaughnessy's trial demonstrated a survival advantage of approximately three months for the addition of capecitabine to docetaxel in the metastatic setting for anthracycline-refractory patients. This was a well-conducted, statistically rigorous trial, and the results are certainly believable.

Capecitabine provides a real benefit for patients with metastatic breast cancer, but I don't conclude that combination therapy is superior to sequential single-agent therapy, and this trial did not test that hypothesis. There was no crossover arm from docetaxel to capecitabine or from capecitabine to docetaxel. In most cases, patients did not cross over to capecitabine. This trial is not comparable to ECOG-1193, which specifically addressed that question.

— George W Sledge, MD

The big question associated with the sequential single-agent versus combination chemotherapy trials is the effect of crossover therapy. In Joyce O'Shaughnessy's trial, we don't know what the effect on survival would have been if 60 or 70 percent of the patients treated with single-agent docetaxel were then treated with capecitabine. Maybe we would not have seen a survival difference. Hence, the effect of crossover therapy remains a question in all of these trials comparing doublets to single-agent regimens.

I generally prefer single-agent chemotherapy, but I discuss combination chemotherapy with my patients and offer them a choice. In clinical practice, my approach has been to use combination chemotherapy when I can't wait for a response.

In the patient with limited disease who needs chemotherapy, in whom I'm hoping to obtain a complete remission, consolidate the sites of disease with radiation or if there is a chance for a prolonged remission, I would probably also favor combination chemotherapy.

If the treatment is strictly for palliation or to try to control the cancer, I'm probably going to use sequential single-agent chemotherapy.

— Stephen E Jones, MD

FIGURE 42

Taxanes and Allergic Reactions

Have you observed an allergic reaction to...

Paclitaxel (mean)	36%
Docetaxel (mean)	28%

What percent of your breast cancer patients experience allergic reactions to...

Paclitaxel (mean)	7%
Docetaxel (mean)	4%

FIGURE 43

Taxanes and Allergic Reactions

What allergic reactions have you observed with taxanes?

Side-effect	Paclitaxel	Docetaxel
Hives	23%	31%
Hypotension	44%	32%
Shortness of breath	45%	47%
Wheezing	26%	19%

EDITOR'S COMMENT

Approximately one-third of oncologists have observed allergic reactions to either docetaxel or paclitaxel, but this only occurs in a small fraction of patients. The spectrum of allergic symptoms observed in patients receiving paclitaxel is very similar to those observed in patients receiving docetaxel.

Related Comments from Research Leaders

A significant incidence of hypersensitivity reactions (HSRs) has been associated with paclitaxel. HSRs first were observed during phase I clinical trials.

Prior to the advent of premedications, the incidence was estimated as high as 10%–16% and currently is estimated to be 1%–3%.

Paclitaxel-related HSRs occur rapidly, typically during the first 10 minutes to an hour of the infusion. Signs and symptoms may include any or all of the following: respiratory distress, hypotension, angioedema, flushing with urticaria, bronchospasm, diaphoresis, hypertension, and chest or back pain. Facial flushing alone is not an indication for stopping the infusion.

— Myers JS.
Clin J Onc Nurs 2000;4(4):161-3.
[Citations omitted]

Docetaxel, despite not being formulated in cremophor, is commonly associated with the development of hypersensitivity reactions. Fortunately, as with paclitaxel, these events rarely result in discontinuation of treatment.

Standard prophylaxis against docetaxel hypersensitivity reactions differs from that used with paclitaxel, patients routinely receiving several oral doses of dexamethasone (for 3-5 days) rather than a single intravenous administration of corticosteroids in combination with histamine-blocking agents. This procedure also protects patients against the development of docetaxel-associated fluid retention. ...

For those individuals who develop manifestations of immediate-type hypersensitivity [to paclitaxel] (eg, hypertension, hypotension, diffuse erythema, severe anxiety, dyspnea), it is now recognized that 90% can be successfully treated with the agent if the infusion is quickly discontinued when the initial signs/symptoms are observed (almost always <1-2 min after initiation of the paclitaxel infusion) and then restarted approximately 30 min later.

This is presumably because the initial reaction depletes the immune system of relevant mediators of hypersensitivity (eg, "mast cell degranulation"), which then take some poorly defined period of time to recover sufficiently to result in a subsequent reaction.

— Markman M.
Support Care Cancer 2003;11(3):144-7.

The paclitaxel vehicle CrEL has been shown to influence the toxicity, pharmacokinetics, and antitumor activity of paclitaxel. With regard to paclitaxel-induced HSR [hypersensitivity reactions], CrEL is probably responsible, because other drugs formulated with it produce similar reactions, and CrEL-free paclitaxel does not cause HSR. Likewise, a growing body of evidence shows that CrEL itself is closely related with peripheral neuropathy, one of the main side effects reported for paclitaxel chemotherapy.

— Kim TY et al.
Clin Cancer Res 2004;10(11):3708-16.

FIGURE 44

Premedication and Taxanes

When utilizing taxanes, which premedications do you use?

Antihistamines	72%
Corticosteroids	94%
Antiemetics	36%
Other	42%

Which best describes your use of steroid premedication?

	Paclitaxel	Docetaxel
Always	86%	86%
Frequently	10%	10%
Occasionally	0%	2%
Never	2%	2%

FIGURE 45

Steroid Premedication-associated Toxicities

What percent of patients experience the following from steroid premedication?

Side-effect	Paclitaxel	Docetaxel
Any problem	18.7%	17.7%
Diabetes	12.9%	13.1%
Fluid retention	9.3%	12.2%
Mental changes	5.4%	5.9%

EDITOR'S COMMENT

The clinical use of taxanes requires combination preventive agents. The use of corticosteroids is virtually universal. Oncologists estimate that almost 20 percent of patients receiving either docetaxel or paclitaxel experience significant side effects of toxicities associated with the use of premedication with corticosteroids. The most common problem is the onset or exacerbation of diabetes.

Related Comments from Research Leaders

Patients receiving taxane therapy require premedication to minimise the risk of hypersensitivity reactions. However, the premedication guidelines recommended for paclitaxel and docetaxel are markedly different. Patients who receive paclitaxel require both intravenous histamine H1 and H2 antagonists in addition to oral corticosteroids before 1-, 3- or 24-h infusions, although there is some evidence that premedication is not needed before prolonged infusions (those exceeding 96 h).

By contrast, the premedication regimen recommended for patients receiving docetaxel consists of 3 days' oral dexamethasone (8 mg twice daily).

— Guastalla J et al. Br J Cancer 2003; 89(Suppl 3):16-22.

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Biganzoli, L et al. **Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial.** *J Clin Oncol* 2002;20:3114-21. Abstract

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Wildiers H, Paridaens R. **Taxanes in elderly breast cancer patients.** *Cancer Treat Rev* 2004;30(4):333-42. Abstract

Wist EA et al. **Weekly one-hour paclitaxel as first-line chemotherapy for metastatic breast cancer.** *Acta Oncol* 2004;43(1):11-4. Abstract

FIGURE 46

Sequencing Endocrine Therapy

How do you normally sequence endocrine therapy in postmenopausal patients with metastases and no prior endocrine therapy?

Therapy	First-line	Second-line	Third-line	Fourth-line
Tamoxifen	18%	36%	12%	12%
Anastrozole	36%	16%	4%	2%
Letrozole	46%	4%	8%	2%
Exemestane	–	22%	36%	10%
Fulvestrant	–	20%	36%	32%
Megestrol acetate	–	–	4%	10%

FIGURE 47

Sequencing Endocrine Therapy

How do you normally sequence endocrine therapy in postmenopausal patients with metastases who completed adjuvant tamoxifen four years previously?

Therapy	First-line	Second-line	Third-line	Fourth-line
Tamoxifen	8%	12%	10%	12%
Anastrozole	44%	10%	4%	–
Letrozole	48%	6%	2%	4%
Exemestane	–	34%	30%	6%
Fulvestrant	–	38%	36%	14%
Megestrol acetate	–	–	4%	16%

EDITOR'S COMMENT

The recent availability of aromatase inhibitors and the estrogen receptor downregulator fulvestrant has complicated the algorithm for management of metastatic breast cancer in postmenopausal women.

A key issue is previous use of adjuvant endocrine intervention, and for patients with no prior treatment, the nonsteroidal aromatase inhibitors are clearly first-line therapy. In this situation, tamoxifen followed by fulvestrant or exemestane are the next agents utilized.

For postmenopausal women who have previously received adjuvant tamoxifen, nonsteroidal aromatase inhibitors are generally first-line therapy, which is then followed by either fulvestrant or exemestane.

Related Comments from Research Leaders

If you look at the data recently published in the *Journal of Clinical Oncology* in the ER-positive subset, fulvestrant and tamoxifen were basically equivalent. If you evaluate all the patients, fulvestrant demonstrated some numerical inferiority.

One factor you might consider in selecting a hormonal agent is that some patients actually like monthly intramuscular injections as opposed to daily oral therapy. If you asked most oncologists, they would say, "Patients prefer an oral treatment." However, there is a substantial minority that would prefer to get a shot every month.

— Richard M Elledge, MD

In the first-line study, in the ER/PR-positive group, fulvestrant was slightly (but not significantly) better than anastrozole.

We have to ask, "Why wasn't fulvestrant better than tamoxifen?" That's what we expected. The answer may be in the dosing of fulvestrant, because it takes about six months to achieve steady-state levels. Clinical trials will evaluate loading-dose schedules of fulvestrant. Our modeling analyses indicate these approaches will increase the dose of the drug sooner, and then we will be able to investigate whether that is the reason fulvestrant was not better than tamoxifen in the first-line trials.

— Anthony Howell, MD, MSc, FRCP

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

In this country, fulvestrant is often used as a third- or fourth-line hormonal therapy; however, studies indicate that it might be better than anastrozole following disease progression on tamoxifen. I encourage physicians who are going to try fulvestrant to use it in women progressing on tamoxifen.

— Stephen E Jones, MD

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

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

— Robert W Carlson, MD

Fulvestrant 250 milligrams is an effective dose, as demonstrated by the clinical trials. It is as effective as anastrozole as second-line therapy and equivalent to tamoxifen as first-line therapy in postmenopausal women. In premenopausal women, data suggest that 250 milligrams of fulvestrant is not effective at downregulating the estrogen receptor. This raises questions about whether a 250-milligram dose of fulvestrant leads to complete downregulation of the estrogen receptor in postmenopausal women. Could a higher dose of fulvestrant achieve more?

Two strategies exist to increase the dose of fulvestrant. The first is a loading dose sequence. The second is the administration of a higher dose of fulvestrant. For example, instead of administering one five-milliliter injection every month in one buttock, once could use a five-milliliter injection in each buttock, for a total of 500 milligrams. Future studies are needed to determine the dose-response curve for fulvestrant.

— John FR Robertson, MD, FRCS

In patients with hormone receptor-positive disease progressing on tamoxifen, one can switch to an aromatase inhibitor and there's a good chance the patient will respond. Three commercially available agents have been studied and are approved in this setting, so which agent to use is up to the individual oncologist.

Fulvestrant is also a good choice for these patients. In the two randomized studies comparing it to anastrozole, fulvestrant performed at least as well if not slightly better than anastrozole. Hopefully these patients will benefit from hormonal therapy for an extended period of time, and either fulvestrant followed by an aromatase inhibitor or the other way around will be reasonable alternatives.

— Eric P Winer, MD

For postmenopausal women, a wide choice of endocrine treatment options is available and an optimal sequence has yet to be determined. Options for first-line therapy of metastatic disease include an AI for women who have received adjuvant tamoxifen or tamoxifen for patients who have received adjuvant anastrozole. In addition, data suggest that fulvestrant ('Faslodex'), a novel estrogen receptor (ER) antagonist that downregulates the ER protein and has no known agonist effects, is a promising therapeutic option that has shown efficacy in the treatment of postmenopausal women with advanced breast cancer. Other agents that may be used in the sequence include the steroidal AI exemestane and the progestin megestrol acetate. The widening range of adjuvant endocrine options therefore represents an opportunity to prolong patient benefits in the treatment of hormone receptor-positive breast cancer, and will require the further refinement of the optimal sequence of endocrine agents for the treatment of recurrent breast cancer.

— Carlson RW, Henderson IC. Breast Cancer Res Treat 2003;80(Suppl 1):19-26.

In an open-label trial, there were no significant differences between letrozole and anastrozole for the clinical end points of time to progression (primary end point), time to treatment failure, overall survival, clinical benefit, duration of clinical benefit, time to response, duration of response or objective response rate in patients with confirmed hormone receptor-positive tumours. Together these data suggest that once a certain threshold of aromatase inhibition is reached, small differences in oestrogen suppression between the third-generation AIs do not lead to clinically significant differences in overall efficacy.

— Sainsbury R. Br J Cancer 2004;90:1733-39.

We aim to address whether hormone receptor status influences treatment outcome in postmenopausal women receiving aromatase inhibitors for advanced breast cancer. We include data from three phase III clinical trials, comparing the activity of the new-generation aromatase inhibitors, anastrozole or letrozole, with tamoxifen as a first-line treatment.

For both agents, a significant relationship was observed between hormone receptor status and TTP, with increased TTP seen in patients with a higher confirmed percentage of ER- and/or PR-positive tumors. A relationship between objective response rate (complete or partial response) or clinical benefit (complete or partial response or stabilization for >/=24 weeks) and hormone receptor status was apparent for anastrozole but not letrozole treatment.

— Buzdar AU et al. Breast J 2004;10(3):211-7.

FIGURE 48

Sequencing Endocrine Therapy

How do you normally sequence endocrine therapy in postmenopausal patients who develop metastases while receiving adjuvant anastrozole?

Therapy	First-line	Second-line	Third-line	Fourth-line
Tamoxifen	40%	20%	6%	4%
Anastrozole	2%	–	2%	–
Letrozole	6%	6%	4%	6%
Exemestane	20%	22%	22%	4%
Fulvestrant	32%	36%	16%	6%
Megestrol acetate	–	4%	12%	6%
High-dose estrogen	–	–	–	4%

EDITOR'S COMMENT

A new generation of patients is emerging who develop metastatic disease while receiving adjuvant nonsteroidal aromatase inhibitors (mainly anastrozole). For these patients, tamoxifen, exemestane and fulvestrant are utilized at first relapse.

Related Comments from Research Leaders

Selection of a hormonal therapy after a patient relapses on anastrozole is a problem. Tamoxifen or fulvestrant could be highly effective, but if the MAP kinase pathway is overdriven from the aromatase inhibition, tamoxifen might act more as an agonist, and fulvestrant might be a better choice.

To my knowledge, in terms of ATAC or other patients who have relapsed on an adjuvant aromatase inhibitor, no data have yet addressed this issue.

— Paul E Goss, MD, PhD, FRCP(CA), FRCP(UK)

A couple of reports have evaluated the response to fulvestrant in patients who have received an aromatase inhibitor. A fairly small Swiss study reported that about one-third of patients derived clinical benefit from fulvestrant after treatment with tamoxifen or an aromatase inhibitor.

A compassionate-use study, reported at ASCO 2003, reported about 60 patients with fulvestrant as second-, third- or fourth-line therapy. Fulvestrant had more than a 50 percent clinical benefit rate in those patients.

The sequencing paradigm will probably shift because more patients will be treated with adjuvant anastrozole. We don't know where fulvestrant will fit into that sequence in a patient who has never received tamoxifen and whose disease relapses after adjuvant anastrozole.

— Stephen E Jones, MD

Hormonal agents have a confirmed role in the management of postmenopausal women with receptor-positive advanced breast cancer. Until recently, tamoxifen has been the accepted agent for treating these patients. However, accumulating evidence suggests that the new antiaromatase agents will replace the antiestrogens as the preferable option in hormone-naive patients.

Comparative trials indicate that the aromatase inhibitors, anastrozole and letrozole, and the aromatase inactivator, exemestane, have at least equivalent efficacy to tamoxifen with similar or superior tolerability.

These agents are also more effective than the progestin, megestrol acetate, when studied in patients progressing on tamoxifen. The improved aromatase selectivity and high potency of these antiaromatase agents when compared with earlier agents have resulted in improved efficacy and tolerability.

Additionally, no cross-resistance has been reported between the antiaromatase agents and tamoxifen or, in some instances, among the antiaromatase agents themselves.

— Vogel CL.
Anticancer Drugs 2003;14(4):265-73.

The endocrine cascade for the treatment of premenopausal women with metastatic disease now involves the concurrent or sequential combination of a luteinizing hormone-releasing hormone analogue and tamoxifen, whereas the cascade for the treatment of postmenopausal women can begin with tamoxifen followed by an aromatase inhibitor or with an aromatase inhibitor followed by tamoxifen.

The optimal cascade following the use of an aromatase inhibitor and tamoxifen in postmenopausal women remains unclear, but fulvestrant and megestrol acetate or the use of an aromatase inactivator (exemestane) following an aromatase inhibitor are all available options with some activity. Over the next few years, clinical trials will clarify the optimal sequence of endocrine therapy for postmenopausal women.

— Pritchard KI.
Clin Cancer Res 2003;9(1 Pt 2):460S-7S.

FIGURE 49

Actual Case From Practice: Last Postmeneopausal Patient with Reccurence on Adjuvant Tamoxifen, Treated with Endocrine Therapy

Median age: 68

Other significant medical conditions	24%
Sites of metastases	
Lung/pleura	28%
Bone	80%
Liver	14%
Cancer-related symptoms	
None	22%
Bone pain	60%
Other pain	14%
Respiratory	16%

FIGURE 50

Actual Case From Practice: Last Postmeneopausal Patient with Reccurence on Adjuvant Tamoxifen, Treated with Endocrine Therapy

Which endocrine therapy did you utilize?

Anastrozole	40%
Letrozole	42%
Exemestane	2%
Fulvestrant	16%

EDITOR'S COMMENT

To obtain a more accurate assessment of this important issue, we asked these oncologists to discuss the last woman in their practice who developed disease recurrence while receiving adjuvant tamoxifen. Approximately one-fourth of these women had significant comorbid conditions, and more than three-fourths had tumor-related symptoms.

Although randomized clinical trials have demonstrated at least an equivalence of aromatase inhibitors and fulvestrant in this situation, most of these patients were treated with a nonsteroidal aromatase inhibitor. The likely rationale for this choice is avoidance of the intramuscular injection.

Related Comments from Research Leaders

When I see a postmenopausal patient who has relapsed on adjuvant tamoxifen, I tend to use an aromatase inhibitor followed by fulvestrant when the disease progresses. In the frontline metastatic trials of aromatase inhibitors versus tamoxifen, data demonstrate that regardless of whether you administer an aromatase inhibitor after tamoxifen or tamoxifen after an aromatase inhibitor, the result is a 40 to 50 percent clinical benefit rate.

In the second-line setting, if you administer fulvestrant after an aromatase inhibitor or an aromatase inhibitor after fulvestrant, the result is approximately a 33 percent clinical benefit rate. These are all small trials and most of them are not randomized, but they show that any of these regimens can be effective and no mandatory sequence exists for these agents.

— Joyce O'Shaughnessy, MD

The third-generation AIs, anastrozole and letrozole, have been shown to be as effective or more effective than megestrol acetate and tamoxifen as second- and first-line therapies for the treatment of postmenopausal patients with metastatic breast cancer, and exemestane has been approved for second-line use. Fulvestrant has been shown to be as effective as anastrozole as second-line therapy for metastatic breast cancer and has been approved in the US for the treatment of postmenopausal women with hormone-receptor-positive metastatic breast cancer following progression on antiestrogen therapy.

— Buzdar AU. The Oncologist 2003;8:335-41.

In the metastatic setting, letrozole and anastrozole appear to be very similar in both effectiveness and toxicity. Exemestane has not been very well-evaluated, but I would wager that the results will be similar. In the metastatic setting, I don't have much of a preference for one aromatase inhibitor versus another. There's been a lot of speculation that letrozole may lead to some amount of adrenal insufficiency. I'm not sure whether that will be true. Exemestane may have a superior safety profile in terms of bone, but we should think about its potential steroidal effects.

— Genererosa Grana, MD

FIGURE 51

Use of Selective Estrogen Receptor Downregulators	
Have you prescribed fulvestrant?	
Yes	98%
For those answering "yes," in how many patients?	
Mean	9.5
What percentage reported difficulty tolerating the injection?	
Mean	6%
What percentage reported significant side effects?	
Mean	3%

EDITOR'S COMMENT

Almost all oncologists now have experience prescribing fulvestrant, which is associated with very few side effects or problems tolerating the injection.

Related Comments from Research Leaders

In my clinical experience, fulvestrant is very easy to administer and extremely well-tolerated. My patients have not had any problems with the intramuscular injection. One might assume that a pill is more convenient therapy for a patient than an injection, but that is not necessarily so. Convenience is an individual choice. Some patients would rather receive a shot once a month than take a pill every day. Not only has fulvestrant been exceptionally well-tolerated, I've seen responses in heavily pretreated patients. Fulvestrant also works after multiple endocrine failures, including tamoxifen and the aromatase inhibitors, even in a third- or fourth-line setting. We now have a very well-tolerated endocrine agent to add to our armamentarium in the metastatic setting.

— Richard M Elledge, MD

I've used a fair amount of fulvestrant, and it's very well-tolerated. We've had some very nice responses to fulvestrant, including one of my patients who was on the original clinical trial of fulvestrant versus anastrozole. She was on fulvestrant for three and a half years and now she's on anastrozole. The injections have not been an issue for patients, and most women are very grateful that the side-effect profile is close to nil. I think fulvestrant probably crosses the blood-brain barrier and patients do have hot flashes on it, but in general, they're quite mild.

— Joyce O'Shaughnessy, MD

This was the first randomized trial to compare the efficacy and tolerability of fulvestrant, the new ER antagonist, with tamoxifen for the treatment of postmenopausal women who have received no prior hormonal or cytotoxic therapy for advanced breast cancer. …

Fulvestrant showed neither superiority nor noninferiority to tamoxifen for the primary efficacy end point of TTP. The almost identical median TTP for fulvestrant and tamoxifen (approximately 8 months) in the subgroup of patients with ER and/or PgR tumors (the group intended for treatment with endocrine therapies) indicates similar efficacy for the two treatments against hormone receptor-positive tumors.

— Howell A et al.
J Clin Oncol 2004;22:1605-13.

Comparative data concerning the efficacy, toxicity, tolerability and cost of AI vs tamoxifen continues to evolve with over 40 000 women slated to be involved in clinical trials. Currently, tamoxifen remains an appropriate choice for adjuvant treatment, and will remain so unless a clear survival advantage emerges for adjuvant AI therapy. However, anastrozole is widely seen as a useful alternative, with particular merit for patients prone to the development of serious tamoxifen side effects. For endocrine therapy naïve advanced disease, several trials have provided evidence that a nonsteroidal AI has replaced tamoxifen as optimal treatment.

— Wong ZW, Ellis MJ.
Br J Cancer 2004;90:20-5.

One of the crucial issues in breast cancer today is how best to integrate the various hormonal therapies. We now have a panoply of hormonal therapies available: antiestrogens, aromatase inhibitors, a pure antiestrogen that knocks out the estrogen receptor and the old progestins.

I suspect we'll shuffle between these agents once we have a better understanding of cell phenotypes. Then we'll be able to identify the appropriate hormonal therapy for each patient and tailor our treatment before we see actual clinical resistance.

In the metastatic setting, I generally use an aromatase inhibitor first, then an antiestrogen and then fulvestrant. Unless there's a contraindication, I begin with aromatase inhibitors because I believe sufficient evidence indicates that they are better than tamoxifen for front-line therapy in metastatic disease. I see approximately a 10 percent incidence of articular complaints with aromatase inhibitors, but I've found that switching the structure from a nonsteroidal to a steroidal aromatase inhibitor, or vice versa, seems to diminish those complaints.

— Daniel R Budman, MD, FACP

FIGURE 52

Actual Case From Practice: Last Patient Receiving Fulvestrant

Median age: 68

Years since original diagnosis:

>10 years	10%
7 to 10 years	22%
4 to 6 years	32%
1 to 3 years	36%

How long has the patient currently been on fulvestrant?

Mean	5.9 months

FIGURE 53

Actual Case From Practice: Last Patient Receiving Fulvestrant

Which prior adjuvant endocrine therapy did the patient receive?

Tamoxifen	54%
Anastrozole	6%
Letrozole	6%

Did the patient have significant comorbid medical problems?

Yes	14%

What were the major sites of metastatic disease?

Bone	74%
Lung/pleura	30%
Liver	24%

Was the patient having cancer-related symptoms?

Yes	84%

For those answering "yes," which symptoms?

Bone pain	64%
Other pain	8%
Pulmonary	14%

EDITOR'S COMMENT

To better assess how fulvestrant is utilized, we asked the physicians to describe the last woman in their practice treated with this agent. On average, patients had been receiving fulvestrant at that point for about six months.

Most of these patients had tumor-related symptoms, and many had received prior adjuvant endocrine therapy.

Related Comments from Research Leaders

Retrospective data suggest that fulvestrant may have a longer duration of response than anastrozole. It's an interesting finding that would support some of the preclinical models. However, as academic clinicians, we need to be rigorous in our review of the data.

Our group has some patients who have had long durations of response to fulvestrant. One woman was on fulvestrant for more than seven years, another for more than five years and another for four and a half years. We've also reported good responders who were treated with other hormonal agents. The only way to test whether patients treated with fulvestrant have longer durations of response is by conducting a randomized trial.

— John FR Robertson, MD, FRCS

Extending the period during which endocrine therapy may be used as an effective and viable treatment option for advanced or metastatic breast cancer in postmenopausal women is an important goal. No curative treatment is currently available for many of these patients, and the ability of endocrine therapy to induce responses without producing debilitating toxicities is very valuable….

This report represents the first examination of sequential endocrine therapy incorporating the ER antagonist fulvestrant before AIs. The results demonstrate that after sequential treatment with tamoxifen and fulvestrant, many patients retain sensitivity to further endocrine therapy with third-generation AIs such as anastrozole and letrozole, or progestins such as megestrol acetate. The rates of CB reported here with endocrine therapy after fulvestrant are similar to those reported for therapy with other endocrine agents (30 to 50 percent).

— Vergote I et al. Breast Cancer Res Treat 2003;79:207-11. [Citations omitted]

FIGURE 54

Actual Case From Practice: Last Patient Receiving Fulvestrant

How did this woman receive the fulvestrant injection?

Two 2.5-cc injections	57%
One 5.0-cc injection	43%

Was the patient receiving bisphosphonates?

Yes	70%

Has the patient had any side effects from treatment?

Yes	22%

For those answering "yes," which side effects?

Hot flashes	6%
Injection site discomfort	16%

EDITOR'S COMMENT

About half of these patients were treated with a single intramuscular injection of fulvestrant as opposed to split injections, and most patients were also receiving intravenous bisphosphonates and were therefore already committed to a monthly visit to the oncologist's office. Most of these patients were not experiencing side effects from fulvestrant, but a minority reported discomfort from the injection.

Related Comments from Research Leaders

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

— Robert W Carlson, MD

It's great to have fulvestrant as another option for patients who progress following adjuvant tamoxifen, as well as for patients with whom compliance or availability of drugs is an issue. Also, in patients receiving drugs such as pamidronate or zoledronate for bone metastases, the fulvestrant injection can be administered when they come in for treatment so we know they're receiving adequate care. In terms of tolerability of the injections, I have observed absolutely no problems with them and have received almost no complaints from patients who are receiving the medication. Hot flashes can be difficult to control in many women who have had prior hormone replacement therapy, and I find they're equivalent whether the patient is taking anastrozole or fulvestrant in the metastatic setting.

— Leroy M Parker, MD

Hormonal therapy (HT) is an important consideration in the management of postmenopausal women with metastatic breast cancer. Despite the fact that the advanced-stage disease is virtually incurable, HTs can offer patients disease control equivalent to that of chemotherapy, but with improved quality of life (QOL)….

Disease that becomes refractory to an initial HT may respond to another agent or class of HTs. Thus, HTs are generally administered sequentially, delaying the need for cytotoxic chemotherapy, which often reduces QOL. Optimal sequencing is thus one of the more important facets of HT. Prior to the release of a number of newer agents, tamoxifen had been considered as initial HT. At present, more agents exist, including the aromatase inhibitors, progestins, and the estrogen receptor antagonist fulvestrant.

— Parker LM.
Clin Ther 2002;24 Suppl C: C43-57.

Following relapse on endocrine therapy for advanced, hormone receptor-positive breast cancer, it is common for patients to experience responses to alternative endocrine agents. Fulvestrant ('Faslodex') is a new type of endocrine treatment — an oestrogen receptor (ER) antagonist with no agonist effects. Fulvestrant downregulates cellular levels of the ER resulting in decreased expression of the progesterone receptor. This unique mode of action means that it is important that fulvestrant is placed optimally within the sequence of endocrine therapies to ensure that patients gain maximum benefit. Fulvestrant has shown efficacy when used after progression on tamoxifen or anastrozole in postmenopausal women with advanced breast cancer. After progression on fulvestrant, subsequent endocrine treatments can produce responses in many patients, demonstrating that fulvestrant does not lead to crossresistance with other endocrine therapies. Responses to fulvestrant have also been observed in patients heavily pretreated with prior endocrine therapy. Fulvestrant is a versatile endocrine agent that may be integrated into the therapeutic sequence prior to, or subsequent to, other hormonal therapies…

— Johnston S.
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FIGURE 55

Method of HER2 Testing in Specific Cases

In this patient, how was her HER2 status tested?

Case	Timing of HER2 Testing	FISH	IHC	IHC/FISH Confirmation
A	~ Five years ago (patient on TAM for five years)	3%	94%	3%
B	~ One to three years ago (patient on TAM for one to three years)	31%	63%	6%
C	Many years ago (ER-positive mets)	24%	72%	4%
D	~ Six months ago (adjuvant node-positive/ER-positive)	45%	45%	10%
E	~ Six months ago (adjuvant node-negative/ER-positive)	39%	57%	4%
F	Currently (HER2+ treated for mets)	41%	13%	36%

EDITOR'S COMMENT

One of the fascinating and unexpected findings of this survey is related to HER2 testing. We asked these physicians to select six patients from their practices in a variety of situations. As a routine part of the data collection, we asked whether the technique utilized was immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). When we first looked at the results, we saw a surprising heterogeneity that was difficult to explain. However, upon further study, what we saw seemed to correlate with both the likely timing of the testing and the rationale for it. Almost all women who were originally diagnosed more than one year ago had undergone IHC testing, but FISH was more commonly used in women diagnosed in the last year (and having adjuvant decisions made). For patients in whom the use of trastuzumab was being considered, FISH testing was utilized exclusively.

Related Comments from Research Leaders

I assume that the tumors with a 3+ score on IHC are truly HER2- positive, and we do not test them further. An IHC score of 3+ is pretty reliable, as long as it is done at a laboratory that performs a lot of assays. If a tumor has a 2+ score on IHC, we test with FISH. Even in patients with an IHC score of 0 or 1+ and other features of excessively aggressive disease, we may do a FISH test.

Both the Intergroup and the NSABP study discovered that smaller community hospitals were overscoring tumors as 3+. Close to 20 percent of the 3+ scores were downstaged when they were reviewed centrally. The Intergroup protocol has now been amended to require that the patients wait for final randomization until there is a central review of their HER2 status.

I think the same things apply to FISH testing. Since FISH testing already tends to be done at more centralized laboratories, we have not yet explored the quality control issues. I suspect there will be a proliferation of FISH testing, and the reagents will go out to all the community hospitals. Even though there is probably less room for interobserver variability, the same issues will apply. I hope as the FISH technology disseminates, people will do these quality control-type studies.

— Debu Tripathy, MD

Whenever we have a new therapy requiring a predictive test, how that therapy performs is dependent on how good the test is at identifying the appropriate target. Both the NSABP adjuvant trial and the Intergroup trial indicated that HER2 testing in centers around the country — both community centers and academic centers — appeared to be less than perfect. Approximately 25 percent of the time, the test that was done in the local hospital — nonacademic institutions and academic institutions alike — couldn't be confirmed at a central testing site.

We need to be careful about where the HER2 testing is performed and view results from less-experienced labs with caution. This is especially important in the adjuvant setting where, unlike the metastatic setting, we have no way of knowing if the treatment is working, and we're committing the patient to a course of therapy.

Also, when we are banking on results from clinical trials, it is critical that we know the testing is accurate. Currently, trastuzumab has no established adjuvant role, but I suspect in the next three to five years we'll learn whether it's an effective adjuvant therapy. Then, accurate testing will be important to correctly identify the patients who will receive the maximum benefit from therapy.

In metastatic disease when the initial HER2 test results and the clinical

situation are inconsistent, one should consider retesting the patient. I've had a number of patients whose tumors were IHC zero, but their clinical presentation was consistent with HER2 amplification, so I retested. In each one of those cases there was not a discrepancy, but still I think it's worth doing. Even if I find a discrepancy only two out of 100 times, I'm doing those two patients a huge service.

— Eric P Winer, MD

Community laboratories don't have the same performance when compared to the "gold standard" of commercial reference laboratories. Therefore, it is important to find out who is doing the HER2 testing. Good clinicians can also take other clinical variables into account to decide about retesting.

A good deal of evidence shows a correlation between the number of cases one analyzes per week with IHC and assay performance, and that's where commercial laboratories win hands down. They do many more tests per week than a small hospital in rural North America. The bottom line is that there is a learning curve with respect to reading IHC stains. To get to the top of the curve you have to read a lot of them, and the only way to do that is to be in a in a big, busy center or in a commercial laboratory.

— Mark Pegram, MD

After laboratories underwent training from the NSABP and became certified, their accuracy went way up. Several things can be done to improve performance and reduce variability. One is to train the interpreter; another is to have the laboratory certified. It's very important that laboratories participate voluntarily in these quality control programs and that they use controls with every assay.

Oncologists need to be more aware of which laboratory performs the tests and who interprets the results, because it can make a huge difference. Whether it's a hospital-based laboratory or a reference laboratory, I think the oncologist should spend a lot of time getting to know their laboratories, which tests they're using and how they read the results and interpret oncology and pathology guidelines.

— Ann D Thor, MD

The NSABP found the discordance rate to be much lower when experienced or certified laboratories are used for HER2 testing. This is really good for clinical care, because HER2 testing is not only being done for patients potentially eligible for clinical protocols, but also in general clinical practice.

— Edith Perez, MD

IHC was all we initially had available for testing, but early on we saw that IHC was flawed. IHC has a false-negative rate of about 18 percent. In a good laboratory, the false-positive rate for IHC is probably a few percent; it goes up to eight percent in general laboratories and was as high as 40 percent in some of the early reported trials.

Mike Press has data demonstrating a 52 percent concordance with the Dako HercepTest™ among Dako-approved pathologists. The College of American Pathologists has done its own study evaluating the concordance between a central laboratory and pathologists in the community. They are seeing similar trends.

— Dennis Slamon, MD, PhD

In our experience, it is highly unusual for the HER2 status to be altered during the development of the cancer. It is also very rare for us to find disagreement between the HER2 status of the invasive disease and the carcinoma in situ in the same patient. This is also true when we compare the primary tumor to the lymph-node metastasis.

In general, the HER2 status is quite similar or the same with only rare exceptions. In some of those exceptions, the morphologic appearance of the metastasis appears to be different, as if the tumor either developed new characteristics or was developed from an independent primary tumor.

— Michael F Press, MD, PhD

If one wants to know whether a patient has the HER2 alteration, one should do FISH testing. One should not do a default IHC and only if the tumor scores 2+, then do FISH. Using that algorithm, patients without the HER2 alteration will be treated with trastuzumab, and other patients with the HER2 alteration may not be treated.

The BCIRG trial we are conducting was designed with FISH as the only criteria for assessing HER2 status. I think the day is coming when FISH testing is the only assay used in the community, and I hope it will be sooner rather than later.

— Dennis Slamon, MD, PhD

Every patient with metastatic breast cancer in my practice has her tumor evaluated for HER2 gene amplification by FISH. Tumors with an IHC score of 3+ should be evaluated by FISH, because they may not have gene amplification. In tumors with an IHC score of 0 or 1+, three percent and seven percent, respectively, will have HER2 gene amplification by FISH. We need to determine HER2 status accurately, because it is a matter of life or death.

— Melody A Cobleigh, MD

To determine a patient's HER2 status, FISH is currently the best method we have in terms of linking outcome with intervention. I believe ascertaining the HER2 status in patients with metastatic breast cancer is mandatory. One can use the primary tissue; however, whenever feasible, one should biopsy metastatic lesions and re-evaluate the HER2 and hormone receptors.

– Nicholas J Robert, MD

FIGURE 56

Interpretation of HER2 Test Results

How would you interpret the following?

	IHC 3+	IHC 2+	IHC 1+
HER2-positive	78%	4%	0%
HER2-positive only with FISH confirmation	22%	96%	48%
HER2-negative	0%	0%	52%

EDITOR'S COMMENT

When queried about their algorithm for HER2 assessment, most physicians employed the approach commonly stated by research leaders — an IHC of 3+ is considered positive, and any other result requires FISH confirmation. However, 22 percent of oncologists require FISH testing even for tumors that are IHC positive.

Related Comments from Research Leaders

We were surprised when we found poor concordance between community and central laboratory testing, in terms of both HER2 protein expression and gene amplification. Perhaps more unexpected, we found poor concordance in terms of FISH testing in a central laboratory compared to the local laboratories. This last fact really came as a surprise, because the prevalent notion regarding FISH was that it was 100 percent accurate.

The data from these 119 cases were so important that we actually changed the eligibility criteria for this large cooperative group trial (NCCTG-N9831). We modified the protocol so that physicians can still conduct HER2 testing based on any technology in their local laboratories. The patient is then enrolled in the study and starts the doxorubicin/cyclophosphamide (AC) portion of the chemotherapy.

During that time, we test the tumor specimens again by the HercepTest™ and the PathVysion™ FISH assay. If we find that neither of those two tests demonstrates HER2 positivity, we send the tumor specimen to another central laboratory to double-check our laboratory at the Mayo Clinic. If the other central laboratory also finds the tumor HER2-negative by both assays, then we notify the physician that the patient really should not participate in the trial.

— Edith Perez, MD

Considerable controversy remains regarding the optimal method to routinely evaluate HER2 status. I won't treat a patient with metastatic breast cancer until I have a FISH assay.

In the June 2002 issue of the *Journal of the National Cancer Institute*, the NSABP and the Intergroup published their experiences with HER2 assessment, and it really cast doubt about our quality control for immunohistochemistry. Until the College of American Pathologists does something to iron out this problem of quality control, I continue to use FISH.

— Charles L Vogel, MD, FACP, PA

Tumors that score 2+ IHC are frequently found to be HER2-negative when tested by FISH. In those patients, I routinely have their tumors retested by FISH. On the other hand, I do not obtain a FISH analysis for tumors that score 3+ on IHC performed at a laboratory where I trust the pathologist.

Because HER2-positive breast cancer has a fairly specific phenotype (ie, steroid receptor-negative, younger age, early relapse), I will retest those types of patients by FISH if I have a two- to three-year-old IHC score of 0 or 1+. If the patient's tumor is IHC-negative and FISH-positive, I treat them with trastuzumab despite the fact that we do not have clinical data for that group of patients. Tumors that are FISH-positive are likely to have ample amounts of HER2 receptors on their cell surface.

We lack quality control for both IHC and FISH. This is analogous to the situation encountered with estrogen receptor testing in the mid- to late 1970s. One wonders how many patients died because they did not receive adjuvant tamoxifen as a result of inadequate estrogen receptor testing. If adjuvant trastuzumab provides a benefit like adjuvant tamoxifen, we may encounter the same problem.

— George Sledge, MD

It really looks like IHC testing should remain in the purview of central reference laboratories. One of the reasons may be that a number of the large reference laboratories are now using digital image analysis for all of their IHC scoring. Digital image analysis takes some of the guesswork out of the interpretation of these IHC assays. Good pathologists can disagree over the difference between a 2+ and a 3+, but a computer can actually read the same slide over and over again and give you the exact same result.

Pathologists actually call up the information on a digital screen to confirm and double check the assay performance. In most of the large studies in which head-to-head comparisons have been done with digital image analysis and FISH for HER2 testing, the concordance rate is about 90 percent.

— Mark Pegram, MD

FIGURE 57

Treatment for *de novo* ER-negative, HER2-negative Metastatic Disease

How would you generally treat a woman presenting de novo *with ER-negative, HER2-positive metastatic disease?*

Regimen	Asymptomatic bone mets	Asymptomatic liver mets	Moderate pain/ bone mets	Very symptomatic visceral mets
Trastuzumab (H) only	21%	2%	0%	0%
H + Chemotherapy	67%	90%	94%	94%
Chemotherapy alone	12%	8%	6%	6%

EDITOR'S COMMENT

Trastuzumab monotherapy has been demonstrated to have significant antitumor activity and is frequently utilized in patients with asymptomatic metastases; however, most oncologists in this survey combine trastuzumab with chemotherapy, particularly in patients with symptoms. Surprisingly, a small yet substantial minority of oncologists do not utilize trastuzumab as part of first-line therapy for these patients even though essentially every research leader would support its incorporation.

Related Comments from Research Leaders

I tend to put patients into three categories—low risk, intermediate risk and high risk. I look at the low-risk category as an opportunity to give trastuzumab by itself. As the risk increases, I add more agents. My double-agent combination has generally been a taxane and trastuzumab, while my three-drug combination has been taxane/platinum/trastuzumab.

If a patient is fairly asymptomatic and doesn't have much disease, I offer her trastuzumab by itself and see how it goes. Anecdotally, I have had some patients do very well with trastuzumab monotherapy. We conducted a trial in which patients had the opportunity to have a lead-in induction with trastuzumab. Patients who had stable disease or better remained on trastuzumab for eight weeks and then received an additional eight weeks of treatment.

In patients who had evidence of progressive disease, paclitaxel and carboplatin were added to the trastuzumab. It was a small trial of 63 patients, but if you look back and see how the patients fared, we didn't lose any ground during those first eight weeks in patients who didn't benefit from trastuzumab.

For a patient who clearly has visceral metastases and is symptomatic, I use the three-drug combination with the platinum included. The other patients fall in the mix, and we discuss which one to start with and how aggressive to be.

— Howard A Burris III, MD

The decision to use trastuzumab sequentially versus concomitantly with chemotherapy is based on issues such as extent of metastatic disease and the time between diagnosis and progression. In a younger, relatively asymptomatic patient with bone metastases and a good performance status, I don't think compelling evidence exists to use both chemotherapy and trastuzumab initially. No randomized trial compares sequential versus concomitant therapy in such a patient, but in other settings comparing sequential versus concomitant therapy with chemotherapy, concomitant therapy doesn't do any better in terms of survival.

Certainly we enounter patients with metastatic disease in whom we feel chemotherapy is indicated, such as patients with significant visceral or life-threatening disease. Given the positive results of the trials in which trastuzumab was added to chemotherapy — improved response rate, time to progression and survival — my approach has been to give trastuzumab with the chemotherapy. Given our recent Phase III trial results, I would use the carboplatin/paclitaxel regimen.

— Nicholas J Robert, MD

If a woman has a hormone receptor-negative tumor, the only strategy we have is chemotherapy, but if the tumor is HER2-positive, then I give chemotherapy with trastuzumab. Oncologists who prefer to begin with an anthracycline-based regimen as first-line therapy for a HER2-positive tumor presumably do so because of a historic belief that everyone needs an anthracycline up front. I don't believe that's true.

We now have a variety of active nonanthracycline-based drugs, and trastuzumab has clearly been shown to improve survival. I think that's the priority, and we should rely on that data rather than falling back on data from the 1970s.

Several published trials showed the response rate to single-agent trastuzumab is on the order of 30 to 35 percent in patients whose tumors are HER2 3+ by IHC or FISH-positive, so monotherapy is a viable option. However, the response rates to chemotherapy plus trastuzumab are typically twice that, so I usually start with a combination.

— Harold J Burstein, MD, PhD

FIGURE 58

Chemotherapy Regimens Used with Trastuzumab

Which chemotherapies do you generally utilize with trastuzumab?

	1st line	2nd line	3rd line
Docetaxel	40%	26%	10%
Paclitaxel	24%	6%	2%
Carboplatin/docetaxel	8%	16%	5%
Carboplatin/paclitaxel	6%	4%	4%
Vinorelbine	14%	34%	33%
Gemcitabine	6%	4%	22%
Other/none	2%	10%	24%

EDITOR'S COMMENT

Taxanes are the most common agents combined with trastuzumab, and although paclitaxel was the agent utilized in the pivotal trial by Slamon et al, docetaxel is more frequently used by clinicians. Vinorelbine is a common second- and third-line choice.

Related Comments from Research Leaders

All of the chemo-trastuzumab regimens produce excellent response rates between 60 and 70 percent. We're going to need an adjuvant-like trial to produce sufficient power to prove that one regimen is superior to another.

Outside of the context of a clinical trial, you can take your pick of weekly paclitaxel, weekly docetaxel, gemcitabine, vinorelbine or carboplatin/paclitaxel in combination with trastuzumab. I make the decision on the basis of toxicity after counseling and discussion with the patient.

— Charles L Vogel, MD, FACP, PA

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

When we began studying trastuzumab plus vinorelbine in our first Phase II trial with about 40 women, the combination was well-tolerated and there was an overall response rate of approximately 70 percent. We then conducted a multicenter Phase II trial of trastuzumab and vinorelbine in 55 patients and were again comforted by the safety and efficacy data.

— Eric P Winer, MD

The addition of carboplatin to trastuzumab/paclitaxel in advanced breast cancer improved both the response rate and time to progression. The primary endpoint was the response rate, which improved from 36 percent with the two-drug regimen to 52 percent with the addition of carboplatin, with a *p*-value of 0.04. We stratified IHC 2+ and 3+ patients, and the response rate in the 3+ patients jumped to 37 percent with the two-drug regimen and to 57 percent with the addition of carboplatin, with a *p*-value of 0.03. FISH data was collected retrospectively and, although the comparison is not powered for significance, we saw a trend similar to that of the IHC 3+ patients — response rates of 39 percent and 59 percent with the two- and three-drug regimens, respectively.

Time to progression was a secondary endpoint in the trial. The time to progression in the trastuzumab/paclitaxel control arm was similar to what was seen in the pivotal trial by Slamon and colleagues. The addition of carboplatin increased the time to progression from 6.9 months to 11.2 months. Looking only at the IHC 3+ patients, we saw a similar improvement (7.2 months increased to 13.5 months); similar results were seen in the FISH-positive patients as well.

We looked at survival, although it was early to do so, as over 120 patients are still alive. The preliminary analysis shows a trend for improvement with the three-drug regimen. In the IHC 3+ patients we saw an improvement in survival, with a *p*-value of 0.06, approaching 0.05, and the FISH-positive population showed a similar trend. It will be important to see if the survival advantage persists.

The trastuzumab/paclitaxel/carboplatin regimen was well tolerated. The only significant difference in toxicity was increased myelosuppression, which we expected to see from adding carboplatin. However, no significant differences were seen in terms of serious complications, such as infectious complications, significant neutropenia or fever. Other toxicities, such as neuropathy, allergic responses, nausea and arthralgias, were comparable in both arms.

— Nicholas J Robert, MD

We've been interested in nontoxic chemotherapy regimens and have done a lot of work with vinorelbine and trastuzumab. That combination tends to be well-tolerated, doesn't cause alopecia or nausea, and I find it appealing for patients who don't want more aggressive chemotherapy.

— Harold J Burstein, MD, PhD

FIGURE 59

Schedule of Trastuzumab

What trastuzumab schedule do you generally utilize?

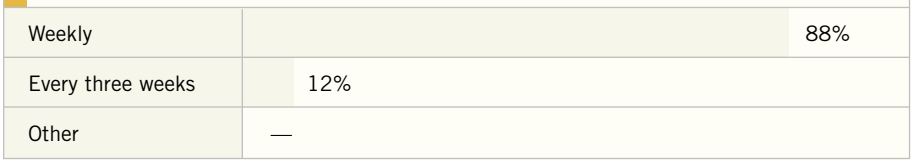

FIGURE 60

Schedule of Trastuzumab and Combination with Endocrine Therapy/Capecitabine

For patients with metastases, have you utilized trastuzumab combined with…

	No	Yes	No. of patients (mean)
Endocrine therapy	40%	60%	9.7
Capecitabine	48%	52%	7.6

EDITOR'S COMMENT

Research from Brian Leyland-Jones has demonstrated the feasibility of using every three-week dosing of trastuzumab, but currently, most clinicians utilize the weekly schedule.

Considerable controversy exists over the role of combining trastuzumab with endocrine therapy. Ongoing clinical trials are evaluating this strategy, particularly the combination of aromatase inhibitors with trastuzumab. A lot of debate has occurred with regard to combining trastuzumab with capecitabine, which does not appear to be synergistic on in vivo testing. Nevertheless, about one-half of oncologists have utilized these combinations in their practices.

Related Comments from Research Leaders

Trastuzumab administered at longer intervals (every three weeks) and at three times the dose is being investigated. Brian Leyland-Jones presented data on paclitaxel with trastuzumab given every three weeks that demonstrated the trough did not go below the desirable level. In fact, the overall area under the curve and the peak concentration are higher without any additional toxicity. This may allow for the convenience of every three-week administration.

I still, however, use weekly trastuzumab. I want a little more toxicity data using it every three weeks. For many drugs, it is the peak level that actually mediates toxicity. That may not be the case with every three-week trastuzumab, but I would like a little longer follow-up, especially for cardiotoxicity.

— Debu Tripathy, MD

We, like many others, have been compelled to switch to triple-dose trastuzumab administered every three weeks. When we discuss Dr Brian Leyland-Jones' results from his pharmacokinetic studies with the triple-dose, every three-week schedule with our patients, many opt for it, and so far we have not had any problems with that schedule. At this point, however, we really do not have comparative data from large randomized trials. Many of the cooperative group studies evaluating trastuzumab are adopting the every three-week, triple-dose schedule.

In the BCIRG adjuvant trastuzumab trial, trastuzumab will be given following chemotherapy on an every three-week schedule. Over the next couple of years, hundreds of patients will be treated with the every three-week schedule and safety data will be collected.

From a theoretical point of view, I am not concerned about efficacy. The peak trastuzumab blood levels are actually higher on the every three-week schedule. Because more trastuzumab is on board, if anything, there could be greater efficacy. I do not believe that will necessarily be the case, but certainly there is no theoretical reason to expect a decrease in efficacy.

— Mark D Pegram, MD

In the subset analysis of the pivotal trastuzumab trial, prior hormonal therapy did not adversely affect the outcomes with chemotherapy and trastuzumab together. For that reason, I feel very comfortable offering endocrine therapy without trastuzumab, as long as it's clinically indicated, and then bringing in the trastuzumab later.

Many clinical trials are evaluating aromatase inhibitors with or without trastuzumab. Everyone expects to increase the response rate and time to progression by adding the trastuzumab early because it's an active drug in and of itself.

However, I assume that these studies are never going to answer whether or not there will be a survival benefit because they are relatively small and weren't designed to have that much follow-up. I think this question will be on the table for a long time.

— Harold J Burstein, MD, PhD

In patients with HER2-positive, ER-positive metastatic breast cancer, I use front-line hormone therapy, assuming

they don't present with life-threatening disease. If the patient responds and then progresses, I continue with endocrine therapy.

If she does not respond initially, then I use trastuzumab monotherapy and add chemotherapy when progression occurs. I haven't used trastuzumab and hormonal therapy together because I'm unaware of in vitro models showing a synergy between these two therapies.

When using trastuzumab as monotherapy or in combination with chemotherapy, I use the every three-week schedule. In terms of chemotherapy, I find the weekly carboplatin/paclitaxel/trastuzumab combination is extremely well-tolerated and active. When a patient presents in visceral crisis, I use either vinorelbine/trastuzumab or weekly carboplatin/paclitaxel/trastuzumab.

— Melody A Cobleigh, MD

We compared a weekly schedule to an every three-week schedule of paclitaxel, carboplatin and trastuzumab in patients with HER2-positive metastatic breast cancer. Tolerability was much better for the weekly schedule. Although I thought this would be the case, I was surprised how great the tolerability was for the weekly regimen. Essentially, we observed no significant toxicity, and the activity was very high.

Our trial fits in very well following Nick Robert's data demonstrating the benefits of adding carboplatin to paclitaxel and trastuzumab, administered once every three weeks.

We presented our results at ASCO 2003. The target accrual for our study was 92 patients, and we will report data on approximately 75 percent of these patients. Because we found the weekly schedule to be better tolerated, after a certain number of patients enrolled, we closed the every three-week arm and continued accrual only to the weekly regimen.

For the weekly schedule, we administered paclitaxel three out of four weeks. I believe it is critically important to take that fourth week off of chemotherapy to really optimize tolerability.

In both arms, we administered the chemotherapy concurrently with trastuzumab for the first six months. Then, at the six-month point, we discontinued the chemotherapy and continued trastuzumab alone — trying to maximize the activity of the interaction of the three drugs while ameliorating long-term toxicities.

— Edith Perez, MD

I still strongly consider hormonal therapy in women with ER-positive, HER2-positive disease; however, evidence suggests that patients with HER2-positive disease may be less likely to respond to hormonal therapy. For that reason, if I were on the fence about using hormonal therapy or moving on to chemotherapy, I would switch to chemotherapy more readily in patients with HER2-overexpressing disease.

When it is time to switch to chemotherapy in patients with HER2-positive disease, most of us believe trastuzumab is the standard of care. The question is whether to use trastuzumab plus chemotherapy or trastuzumab alone. I think in the United States, and certainly in my own practice, trastuzumab plus chemotherapy is more commonly given.

The survival benefit with trastuzumab in the pivotal trial was seen when the combination of chemotherapy and trastuzumab was given up front. Also, there's a sense that response rates, and therefore control of tumor-related symptoms, are higher when chemotherapy is added to trastuzumab.

— Eric P Winer, MD

If a postmenopausal woman with ER-positive, HER2-positive metastatic disease presents with a minimal tumor burden, I will treat her with an aromatase inhibitor initially and wait to use trastuzumab. I usually start with a nonsteroidal aromatase inhibitor — letrozole or anastrozole — and then move on to exemestane or fulvestrant in patients whose disease progresses.

In patients who need chemotherapy, we use a combination of chemotherapy and trastuzumab because the pivotal trial data demonstrated an improvement in survival for the combination.

When the patients are ready to discontinue chemotherapy, we use the next sequential hormonal agent as maintenance therapy in conjunction with trastuzumab. Studies are currently evaluating the effectiveness of trastuzumab in combination with the aromatase inhibitors, and the results will be very interesting.

— Hope Rugo, MD

I use chemotherapy up front in patients with life-threatening or very bulky HER2-positive disease. In these patients, chemotherapy selection depends on their adjuvant treatment. Traditionally we'll start with a taxane and trastuzumab. For patients in visceral crisis or with bulky disease,

I've been adding weekly carboplatin. Although Nick Robert's randomized trial evaluated an every three-week schedule, we see a fair amount of thrombocytopenia with that treatment schedule, so we've been using weekly carboplatin, paclitaxel or docetaxel, and trastuzumab. As soon as the patients have a good response, we discontinue the chemotherapy and continue with every three-week trastuzumab alone.

I also use capecitabine with trastuzumab, and it's been very effective. Patients with HER2-overexpressing disease are often very receptive to capecitabine. So it's important to use that drug as part of the treatment approach for these patients.

— Hope Rugo, MD

FIGURE 61

Cardiac Functioning and Trastuzumab

Have you discontinued trastuzumab because of abnormal cardiac function tests in a patient who was clinically asymptomatic?

No	40%
Yes	60%

For those answering "yes," in how many patients?

Mean	2 patients

Have you discontinued trastuzumab because of clinically abnormal cardiac function?

No	68%
Yes	32%

For those answering "yes," in how many patients?

Mean	2 patients

FIGURE 62

Cardiac Monitoring and Trastuzumab

Do you routinely monitor cardiac functioning in your patients receiving trastuzumab?

No	40%
Yes	60%

For those answering "yes," which test(s) do you use?

MUGA-scan only	82%
Other	18%

For those answering "yes," how often do you assess cardiac functioning?

Every 2-3 months	42%
Every 3-6 months	38%
Other	20%

EDITOR'S COMMENT

Another controversy in the management of patients with HER2-positive tumors relates to cardiac effects of trastuzumab, and a significant fraction of physicians in practice have had patients with cardiac dysfunction diagnosed either clinically or on screening tests.

Considerable heterogeneity exists regarding screening cardiac testing in patients receiving trastuzumab. About one-half of physicians screen their patients — mainly with MUGA scans.

Related Comments from Research Leaders

When trastuzumab was used in combination with an anthracycline, a significant increase in cardiotoxicity occurred. In the pivotal Phase III trial, about half of the patients with cardiotoxicity had class I and II, and the other half had class III and IV.

Doxorubicin alone is known to cause a nine percent incidence of cardiotoxicity. Patients with clinical cardiotoxicity can be treated with diuretics and ACE inhibitors. When they improve, they can continue on trastuzumab. Or, if the trastuzumab is discontinued, their cardiac function can improve.

We believe the cardiotoxicity associated with paclitaxel/trastuzumab was probably a recall phenomenon because of the data from Chuck Vogel's study in patients with HER2-positive disease who did not receive chemotherapy.

Those patients were treated with trastuzumab alone, and the cardiac dysfunction rate was just under four percent. All were subclinical. Trastuzumab by itself, in a population of patients with minimal anthracycline exposure, was not a major cardiotoxin.

— Dennis J Slamon, MD, PhD

We evaluated surveillance MUGAs in one of our trastuzumab and vinorelbine trials. We did a baseline MUGA and then a follow-up MUGA at 16 weeks. Among those patients who had preserved left ventricular ejection fraction (LVEF) of 50 percent or greater at 16 weeks, none of them went on to develop symptoms of heart failure or significant declines in LVEF. By contrast, in two of the patients who had declines in LVEF at 16 weeks, we saw problems.

One actually developed heart failure, and the other had a drop in ejection fraction to about 40 percent. While

this data only applies to that specific regimen, this has become our routine algorithm.

Anecdotally, I have not seen any late-onset heart failure or changes in LVEF after the first few months of trastuzumab-based therapy. In my experience, cardiac changes usually occur in the first two or three months of therapy, so I think if you recheck the MUGA around three and four months and the patient is clinically stable, you don't need to frequently check it again.

— Harold J Burstein, MD, PhD

BCIRG-006 is a multinational, randomized, controlled trial for patients with FISH-positive, early stage breast cancer — either node-positive or high-risk, node-negative disease. Patients are randomly assigned to one of three different treatment arms: AC followed by docetaxel, AC followed by docetaxel/trastuzumab with trastuzumab continued for a total of one year, and trastuzumab/docetaxel with either carboplatin or cisplatin.

For the first time in a large randomized adjuvant study, a nonanthracycline-containing synergistic combination will be put to the test in a very carefully selected patient population. All of the patients must have FISH-positive disease; therefore, I think the trial will define the standard of care for the adjuvant treatment of patients with HER2-positive breast cancer.

The other important component of this trial is safety. A safety data monitoring committee and a specific cardiac safety monitoring committee are monitoring all of the treatment arms in real time, and they have predefined trigger points that call for an interruption in the protocol if any flags for cardiotoxicity occur in the AC followed by trastuzumab/docetaxel arm.

In fact, the study was designed in such a way that the arm can drop out. If we encounter cardiotoxicity problems, we would still have a two-arm study — one arm with conventional chemotherapy and the other arm with trastuzumab/platinum/taxane.

It doesn't appear that cardiac safety is going to be a big issue in the adjuvant trastuzumab trials. Although there was a scare some months ago with the Intergroup trial and one arm was closed temporarily, that arm has reopened and the most recent update, presented by Dr Edith Perez, reveals that the incidence of depressed ejection fractions is the same in all of the arms of the Intergroup trial.

— Mark D Pegram, MD

In January 2002, we received notification of a few patients who developed congestive heart failure on NCCTG-N9831. We did not know if it was a real problem or if we just happened to have a few cases at the same time, so we decided to temporarily halt accrual to the third arm of the trial — AC followed by paclitaxel and concurrent trastuzumab — until we had more time to do two things.

First we had to evaluate the clinical course of those few patients who developed congestive heart failure. Second, we had to analyze the data based on all of the more than 700 patients enrolled up to that point. Eventually we found that only a few patients had developed congestive heart failure and that they had prompt improvements of their clinical symptoms with medication.

We submitted this information to our independent data monitoring committee. Because the cases of congestive heart failure were below the threshold we had established in the protocol in June 2002, it was recommended that we reopen accrual to this third arm of the trial. We meet with our cardiologists on a monthly basis to look at all of the data from this study. We have very good compliance with the cardiac testing we recommend as part of this clinical study.

Based on data in the metastatic setting, trastuzumab is associated with congestive heart failure. In the adjuvant setting, it is going to be a matter of assuring that the incidence of congestive heart failure is low and of working on potential predictors of congestive heart failure.

Trials are being devised to address this issue. We are evaluating hypertension, the patient's age and radiation therapy to the left chest as being predictors of cardiotoxicity. We are also doing quality control to avoid enhancing the potential cardiotoxicity of trastuzumab.

Theoretically, it makes sense that trastuzumab will have a role in the adjuvant setting. However, first we need to finish the clinical trials to prove that point. Then we will have to find ways to ameliorate cardiotoxicity, even if it's only a few percentage points.

We performed very thorough analyses of ejection fractions as part of NCCTG-N9831, and we presented the data at the ASCO 2003 meeting. The specific data are based on the evaluations of ejection fraction after AC chemotherapy.

We have a lot of clinical experience with AC but a scarcity of data regarding its effect on ejection fraction. We found that AC, at a cumulative dose of 240 mg/m^2, had a zero incidence of congestive heart failure but decreases in ejection fraction, which tended to be transient.

Our opinion is that ejection fraction may be an interesting marker, but we don't know if frequent measurements are good in terms of predicting who will develop congestive heart failure.

— Edith Perez, MD

FIGURE 63

Use of Adjuvant Trastuzumab

Have you ever utilized nonprotocol adjuvant trastuzumab?

No	82%
Yes	18%

For those answering "yes," in how many patients?

Median	3 patients

Would you be likely to recommend adjuvant trastuzumab to a 65-year-old otherwise healthy woman with an ER-negative, HER2-positive tumor with 10 positive nodes?

No	82%
Yes	18%

EDITOR'S COMMENT

Clinical research leaders generally do not support the use of trastuzumab as adjuvant therapy outside the context of a clinical trial. The few oncologists who have employed that treatment strategy have done so only in very high-risk cases.

Related Comments from Research Leaders

If someone uses trastuzumab outside of the clinical trial setting, they're essentially shooting in the dark. We do not yet understand the duration of therapy, the schedule to be used in combination with chemotherapy and the potential risks or benefits the patients may derive.

We have several clinical protocols available. I hope that every woman diagnosed with breast cancer tells her physician, "If I have this bad prognosis, I want to participate in the clinical trial that will help answer the question."

The NSABP is also conducting a very good trial, also based on solid scientific principles. The NSABP trial has two arms — AC followed by paclitaxel, and AC followed by paclitaxel concurrent with trastuzumab for three months, followed by trastuzumab alone. The NCCTG trial has three arms. NSABP-B-31 is using paclitaxel once every three weeks, as in CALGB-9344, while N9831 is utilizing weekly paclitaxel.

— Edith Perez, MD

In the nonprotocol adjuvant setting, it's hard to know the right thing to do. I've evaluated patients with high-risk disease — 10 or more positive nodes — in whom I've considered adjuvant trastuzumab therapy off protocol.

I don't want to say that this is something that is widely done at our center — it's infrequent and uncommon. However, the prospects for a patient with that type of disease are really unacceptable.

If you consider that trastuzumab prolongs survival in patients with metastatic disease, biologically there are probably many similarities between high-risk Stage II and advanced disease. Therefore, that would be an interesting patient population to study, and off protocol we have considered such patients for adjuvant trastuzumab therapy.

— Mark D Pegram, MD

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EDITOR'S NOTE

As discussed in the Editor's Note, we asked each of the 150 medical oncologists surveyed to describe a de-indentified case from their practice of a patient with metastatic breast cancer who had an extraordinarily impressive response to systemic therapy. We also asked the treating physician for a comment on the related educational message for this issue. The following are select examples of these cases.

Case History 1:

I first saw this woman 25 years ago when she was 46. She presented with a primary breast tumor and widespread bone mets. We biopsied the breast and a bone met, and both proved to be the same adenocarcinoma. She had radiation therapy to the lumbar spine and a bilateral mastectomy. We then gave CMF chemotherapy, and after six cycles we started megestrol acetate. The woman is alive today without evidence of cancer 25 years later. She stayed on megestrol acetate forever. She must have been on that drug for 20 years, because no one knew what to do, and everyone was afraid to stop. We finally stopped about four or five years ago and she's never had a recurrence.

COMMENT FROM TREATING PHYSICAN:

Normally, people who present with destructive lesions of the bone don't live that long. It's been very dramatic to watch this unfold.

Case History 2:

This 45-year-old woman had extensive metastatic disease to the bones — the spine and basically the whole skeleton. She had severe pain from the boney involvement. She also had mets to the liver, and that caused her to have severe abdominal pain. The tumor was ER/PR-positive, HER2-negative. I treated her with doxorubicin and cyclophosphamide for four cycles, and then I started her on anastrozole. She has also been receiving zoledronic acid every month.

She had a complete response — complete disappearance of all of her tumor. There is no evidence of disease at this time more than two years later, and she continues on anastrozole and zoledronic acid.

COMMENT FROM TREATING PHYSICAN:

This woman had a bad cancer, and the fact that just hormonal therapy — after some chemotherapy — made her disease completely disappear, is very uncommon and not very likely. She was one of my exceptional cases.

Case History 3:

This 83-year-old woman had neglected herself and came in with a large breast tumor and asymptomatic liver and lung metastases. She had a mastectomy and axillary node dissection that showed 14 positive lymph nodes. The tumor was strongly ER- and/or PR-positive and HER2-negative by FISH. She was brought in by her children. She was living alone and hadn't seen a doctor. We put her on letrozole. That's it; she is still receiving it now for almost two years. She's had a near complete remission in her lung and liver metastases and has not had any recurrence on the chest wall.

COMMENT FROM TREATING PHYSICAN:

In someone whom we were treating for palliation, you want to use as benign a treatment as possible, because you're not going to cure the patient, and you want their quality of life to be as optimal as possible. Here we have a drug like an aromatase inhibitor, which has minimal side effects. She responded very well to endocrine therapy. Visceral disease, unless it's galloping along, is no contraindication to hormonal therapy in breast cancer.

Case History 4:

This woman presented at age 52 with a very large breast mass that involved the chest wall and axillary lymph nodes clinically, and she also had extensive bone metastases. She was bedridden and extremely symptomatic and unable to walk because of her bone metastases. The breast mass was ER-positive.

She initially received six cycles of CAF followed by tamoxifen. Amazingly, this lady survived a total of 18 years. The breast mass and bone pain disappeared. She was on tamoxifen for approximately 12 years in remission before she had a relapse. She was ambulatory and went shopping and very much lived a normal life.

COMMENT FROM TREATING PHYSICAN:

This response was excellent in terms of symptom relief and duration of response. The bone metastases were completely painless and she was able to walk again. The duration of response was so long. For 18 years she had an excellent quality of life and was very functional.

Case History 5:

A 65-year-old woman presented with a very large breast mass that had been ignored for a prolonged period of time. It was bleeding and fungating on the chest wall — really large — it had replaced the entire breast. She had a prior stroke from terrible valvular heart disease, which was causing her to throw clots. The stroke left her blind in one eye. She didn't seek medical care until she began throwing clots from her heart disease. We biopsied the breast and it was infiltrating ductal adenocarcinoma, which was ER-positive and moderately differentiated. There was no evidence of metastatic disease, but the surgeon didn't want to operate.

We decided to go forward with neoadjuvant doxorubicin/cyclophosphamide. I started that with some trepidation, but after four cycles we decided to do a mastectomy and lymph node dissection because she had such a terrific response. At surgery you could see the tumor was necrosing but there was still viable tumor left and the lymph nodes were negative. She also decided to go forward with this heart surgery. It was very strange, but we ended up doing everything at the same time. She made it through the heart surgery easily, and the chemotherapy worked really well for the breast cancer.

After that I gave her four cycles of docetaxel, which seemed to consolidate everything, and now I have her on just anastrozole. The other thing that's strange about her is that she has a myeloproliferative disorder, and I never had to worry about her platelets or her red count when I gave her chemo, because they were always really high. She's a little old lady and I can't believe she did this well.

COMMENT FROM TREATING PHYSICAN:

This older patient with multiple medical problems responded to chemotherapy terrifically, and it saved her life. This woman had a lot of reasons to die. She is hypercoagulable from her polycythemia and she had a problem with her heart, she's stroking, and she had cancer that was ignored. It's just unbelievable. These people are still treatable and sensitive to chemotherapy. Everything improved in this woman except her blindness from the stroke.

Case History 6:

A 52-year-old woman with ER/PR-positive, node-positive tumor who previously received mastectomy, CMF and adjuvant tamoxifen for five years presented with chest pain and shortness of breath and was found to have bilateral pulmonary nodules and pleural effusions. I treated her first with letrozole and she had an excellent objective and symptomatic response. She returned to normal function. After five years, she progressed again and has now responded to fulvestrant for more than a year. Her performance status is excellent.

COMMENT FROM TREATING PHYSICAN:

This woman has done extremely well with metastatic disease for six years and has not required chemotherapy. Hormonal manipulation in some patients is an extremely effective palliative treatment and has allowed this woman to function extremely well with an almost normal quality of life.

Case History 7:

A 32-year-old woman presented with inflammatory breast cancer metastatic to the lungs. She came in with shortness of breath and an obvious breast mass. The tumor was ER- and/or PR-positive and HER2 3+.

We treated her with doxorubicin/docetaxel, which resulted in a complete response in the breast and lungs. She then underwent mastectomy. After surgery we gave trastuzumab and tamoxifen. She is still free of cancer five years later and continues with trastuzumab every three weeks and tamoxifen as maintenance. She's leading a normal life. She had toxicity with chemo early on, but now she's doing great.

COMMENT FROM TREATING PHYSICAN:

Traditionally, in the "old days," a patient like this would probably not go for so long free of disease. I think having a drug like trastuzumab really helped her and kept her disease at bay. These targeted drugs can change the natural history of the disease.

Case History 8:

This 72-year-old woman had ignored a breast mass that basically destroyed her right breast and caused it to completely disappear. She also had extensive boney disease and liver mets. The tumor was ER-positive and HER-2 negative by FISH. She refused chemotherapy, so I prescribed anastrozole and she's been on it for about three and a half years. Her bone lesions got better and her liver lesions went away. The breast mass went completely flat to the chest wall, which now looks totally normal.

COMMENT FROM TREATING PHYSICAN:

The fact that she had widely metastatic disease with a huge chest wall mass, and in spite of refusing chemotherapy or surgery, with simple hormonal manipulation, all of the disease virtually disappeared.

Case History 9:

I met this woman when she was 38 years old after she had just been diagnosed with a relapse after adjuvant therapy. She had lymphadenopathy in the mediastinum, with nodes as large as five centimeters. She also had a couple of pulmonary nodules that were about two centimeters and was having a great deal of chest discomfort. The tumor was ER-positive, HER2-negative.

I sent her for radiation and put her on tamoxifen. She had a dramatic shrinkage of her adenopathy, and her pulmonary nodules have almost completely disappeared. She's now been on tamoxifen for four years and feels very well in a continued remission.

COMMENT FROM TREATING PHYSICAN:

Under normal circumstances we would have expected this young lady to have died by now. The hormone sensitivity of her disease, in spite of her young age, is remarkable to me. When I first met her, I had a sinking feeling in my heart. She didn't want to go on chemotherapy if she could avoid it, and it's just amazing how well the tamoxifen has worked.

Case History 10:

This 72-year-old woman had a prior mastectomy with no systemic therapy in the past. She presented with metastases to the bone, liver and lungs. She refused chemotherapy. I treated her with tamoxifen and she had a good response for two years. The tumor then progressed, and she received letrozole with no response. I then used fulvestrant and she had a near complete response that has lasted two years.

COMMENT FROM TREATING PHYSICAN:

Sometimes you cannot predict what will happen with hormonal therapies. In this case, the most impressive response occurred with the third agent used. This case demonstrates that it's worth trying other hormonal therapies even if one doesn't work.

Case History 11:

This 62-year-old woman presented with headaches, double vision and failure to thrive. She had a four-centimeter mass in her breast that was ER/PR-positive, HER-2 negative. A metastatic evaluation revealed brain, lung, bone and liver metastases.

She did not want to undergo chemotherapy or radiotherapy. All she would accept was endocrine therapy, so I used anastrozole. She had an excellent response. Over the first month she stopped deteriorating and stabilized. Then she began to walk, eat and gain a little weight. By about two months she was ambulatory again. She was certainly not back to her old self but was on the way. This lasted about 18 months, and I now have her on fulvestrant. Scans and markers indicate she had an objective response to both anastrozole and fulvestrant.

COMMENT FROM TREATING PHYSICAN:

Despite her extremely poor prognostic factors upon presentation — the extensive metastases — that we would normally associate with poor endocrine response, she had an excellent endocrine response and very dramatic relief of symptoms and improved quality of life for more than two years.

Case History 12:

This 65-year-old woman had neglected a breast mass for several years. She presented with difficulty walking, and was found to have spinal cord compression — she was completely paraplegic and also had lung and bone involvement with mets. She has a huge primary tumor and palpable axillary adenopathy. I treated her with radiation to the spine, trastuzumab, tamoxifen and then chemotherapy with gemcitabine and cyclophosphamide. The lung nodules pretty much disappeared and the breast mass shrank considerably — about 80 to 90 percent shrinkage. The axillary nodes disappeared. She's now able to walk with a walker, and she's regained about 50 percent of her motor strength. Her paraplegia has improved quite a bit.

COMMENT FROM TREATING PHYSICAN:

In my experience, when complete paraplegia is present from tumor spinal cord compression, probably 95 percent of the time the patient doesn't recover enough nerve function to be able to walk. Essentially, it's a life sentence of paraplegia. This woman has an excellent response to radiation, trastuzumab and chemo and was able to regain much of her strength, which is very, very uncommon when the patient has been paraplegic.

Case History 13:

This 45-year-old woman was sent to me because she was having pain in the right upper quadrant of her abdomen and her internist did a CT scan that showed extensive liver metastases. I examined her and found a breast mass that was ER-negative and HER-2 positive breast cancer on biopsy. She had elevated liver function enzymes and bilirubin and metastatic disease to the brain, but she was asymptomatic. She also had lost about 20 pounds in the last month. She had all the criteria for a grave prognosis. We started her on trastuzumab and docetaxel for six cycles and the tumor responded beautifully. There was 90 percent response in her liver by CT scan criteria. She had gained back some of the weight she'd lost and she was 100 percent better than she was when she presented a year ago.

COMMENT FROM TREATING PHYSICAN:

When I started my career 10 years ago, such a patient would probably only live three to four months, given that most of the liver was involved with cancer and she had lost so much weight and had brain metastases. Typically, these patients do not live long. It has been a year and she continues to have an excellent quality of life on trastuzumab, and the tumor is responding beautifully. Now oncologists have more options than just chemotherapy — we have monoclonal antibody treatments like trastuzumab, which can really improve the quality of life and symptoms of women with breast cancer.

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

- Compare and contrast a management strategy for the treatment of cancer patients to that of other community oncologists and cancer research leaders. 5 4 3 2 1
- Discuss cancer management issues for which there is relative agreement and those for which there is heterogeneity 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

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This program is supported by education grants from
American Pharmaceutical Partners Inc, Amgen Inc,
AstraZeneca Pharmaceuticals LP, and Genentech BioOncology.

Sponsored by Research To Practice.

Last review date: July 2004
Release date: July 2004
Expiration date: July 2005
Estimated time to complete: 2.5 hours