Breast Cancer™ UPDATE

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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2 Audio Tapes

2 Audio CDs

Monograph

CME Certified

Breast Cancer™ UPDATE

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How to use this monograph

This is a CME activity that contains both audio and print components. To receive credit, the participant should listen to the CD or tape, review the monograph and complete the post-test and evaluation form. This monograph contains edited comments, clinical trial schemas, graphics and references, which supplement the audio program and the website, **BreastCancerUpdate.com**, where you will find an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**. This regularly updated website also features an extensive breast cancer bibliography, clinical trial links, a "breast cancer web tour" and excerpts from interviews and meetings catalogued by topic.

Breast Cancer Update: A CME Audio Series and Activity

Statement of Need /Target Audience

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances. To bridge the gap between research and patient care, Breast Cancer Update utilizes one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists medical oncologists in the formulation of up-to-date clinical management strategies.

Global Learning Objectives

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment.
- Describe and implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer patients.
- Develop and explain a management strategy for women with ER-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Develop and explain a management strategy for women with ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Counsel ER-positive postmenopausal patients about the risks and benefits of aromatase inhibitors in the adjuvant setting.
- Evaluate the relevance of emerging data on dose-dense chemotherapy to patients.

Issue 2, 2003 of Breast Cancer Update consists of discussions with four research leaders on a variety of important topics including updated results of the ATAC trial, Intergroup trial 9741 evaluating dose-dense chemotherapy, clinical use of capecitabine and recent data on the addition of carboplatin to trastuzumab and paclitaxel in HER2-positive metastatic disease.

Specific Learning Objectives for Issue 2

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

- Counsel postmenopausal patients with ER-positive breast cancer regarding updated results of the ATAC trial.
- Describe the results of Intergroup trial 9741 of dose-dense adjuvant and its implications to patient management.
- Determine the clinical implications of the recent study showing benefit with the addition of carboplatin to trastuzumab and paclitaxel in patients with HER2-positive metastatic disease.
- Consider use of the oral fluoropyrimidine prodrug capecitabine alone and in combination with docetaxel in the metastatic setting.

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Postgraduate Institute for Medicine and NL Communications, Inc. The Postgraduate Institute for Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals, LP
capecitabine	Xeloda®	Roche Laboratories, Inc.
cyclophosphamide	Cytoxan®, Neosar®	Bristol-Meyers Squibb Company,
docetaxel	Taxotere®	Aventis Pharmaceuticals
doxorubicin	Adriamycin®, Rubrex®	Pharmacia Corporation
exemestane phosphate	Aromasin®	Pharmacia Corporation
filgrastim	Neupogen®	Amgen, Inc.
letrozole	Femara®	Novartis Pharmaceuticals
mitoxantrone	Novantrone®	Immunex Corporation
paclitaxel	Taxol®	Bristol-Meyers Squibb Company
pegfilgrastim	Neulasta®	Amgen, Inc.
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals, LP
trastuzumab	Herceptin®	Genentech, Inc.
vinorelbine	Navelbine®	Glaxo Wellcome, Inc.
zoledronic acid	Zometa®	Novartis Pharmaceuticals

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Editor's Note

Candor with Humility

"I'm not an eccentric maverick in my beliefs, and I'm not alone. The difference between most people and me is that I've never been frightened to speak my mind. Speaking out against mammography does not make you popular."

— Michael Baum, ChM, FRCS

As Michael Baum began his William McGuire lecture at the San Antonio Breast Cancer Symposium, there was no doubt in my mind that at some point, he would challenge the audience's belief in a long-held concept. In the last issue of Breast Cancer Update, Gabe Hortobagyi mentioned Baum's 1982 presentation in Jasper, where with only two years of follow-up for the classic NATO trial, he boldly predicted that tamoxifen would soon become standard of care for adjuvant therapy. Over the years, in journal articles, meeting presentations and interviews for this series, Dr Baum has always pushed us to critically evaluate long-held paradigms and beliefs. In his San Antonio presentation — as he states in this interview — he "dared to challenge the Holy Grail of mammography," suggesting the possibility that in some patients, unnecessary biopsy can perturb and stimulate otherwise indolent tumors. His comments were grounded in science and clinical experience, but, undoubtedly, many attendees took great exception to his challenge of not only the medical rationale but also the ethics of current breast cancer screening practices in the United States.

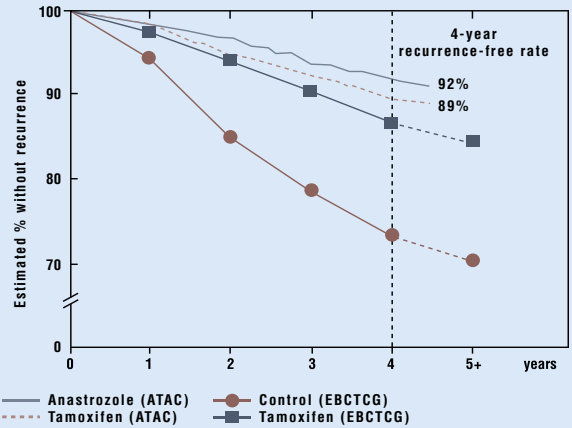
One of the privileges of editing this series is the opportunity to develop longstanding relationships with "movers and shakers" in clinical research. It has been surprising to see how often these people are humble at heart, and Mike Baum is no exception. Last year, I met with him shortly after he presented perhaps the most important initial data set in the recent history of breast cancer research — the ATAC adjuvant trial. During our interview, he was totally at ease, and rather than promote his own role in designing and launching this historic study, he emphasized the dedication of the women who chose to enter the trial. Interestingly, Dr Baum also was very conservative in his approach to translating the data to clinical practice. It was not until recently, one year later with further follow-up, that he began to fully support the use of anastrozole as the first option for adjuvant therapy for postmenopausal women with receptor-positive invasive breast cancer.

I queried a number of research leaders about Dr Baum's comments on breast cancer screening in San Antonio, and most disagreed with the notion that data supports the potentially deleterious effect of mammography on the biology of the disease.

However, there was near universal agreement with Dr Baum's insistence that clinical research on breast cancer screening be held to the same standard as treatment trials. It is also difficult to argue with Dr Baum's demand that the primary care community inform women about the risks and benefits of mammography before they undergo the procedure.

It is quite unlikely that further randomized trials of mammography will be conducted, and as is often the case in clinical practice, we will be left with an imperfect data set from which we must base decisions and recommendations. In that regard, it is interesting to consider a very striking graphic that was presented by Aman Buzdar in San Antonio comparing the ATAC trial results to the most recent findings from the tamoxifen versus control disease-free survival curves from the international breast cancer overview.

Comparison of ATAC data with EBCTCG 1995 Overview Data: Estrogen receptor-positive patients >50 Years

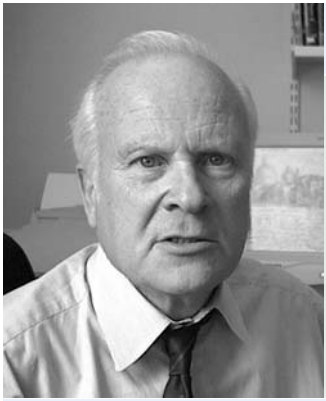


DERIVED FROM: Early Breast Cancer Trialists' Collaborative Group. **Tamoxifen for early breast cancer: An overview of the randomised trials.** *Lancet* 1998; 351: 1451-1467. **Abstract**

The ATAC Trialists' group. **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: 2131-2139. **Abstract**

Dr Buzdar's point is that the ATAC study's data on tamoxifen overlaps the overview data (with anastrozole demonstrating an advantage over both), but within this graphic is a key message about current clinical research. There were more postmenopausal women with estrogen receptor-positive breast cancers in the ATAC trial than there were in the entire international overview of randomized trials of tamoxifen given for five years. Through more than 30 years of randomized trials in breast cancer, we have learned that the most effective way to avoid controversies like the one we see with mammography is to conduct very large, well-designed studies that will help lead to clear cut answers and clinical recommendations.

—Neil Love, MD



Michael Baum, ChM, FRCS

Professor Emeritus of Surgery and
Visiting Professor of Medical Humanities,
University College London

Chair, CRC Breast Cancer Trials Group

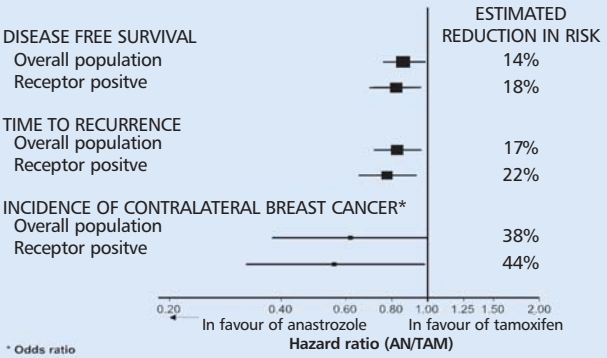
Edited comments by Dr Baum

Updated data from the ATAC trial

The new ATAC trial data gives me comfort and a sense of vindication that we waited a year before starting to make therapeutic recommendations. Last year, I publicly supported the ASCO technology assessment. Last year, I needed persuasion to use adjuvant anastrozole. It was a nice option if tamoxifen could not be tolerated or was contraindicated.

This year, however, with the updated efficacy and safety data, my position has changed. Now, my default therapy for estrogen receptor-positive postmenopausal women is anastrozole unless contraindicated. We have another year of follow-up in the ATAC trial, and I am impressed by the separation of the curves. The safety update is also comforting. The fracture rate isn't racing away, the relative risks are stable and the other safety profile issues strongly continue to favor anastrozole.

ATAC trial 47-month updated efficacy data



DERIVED FROM: A Buzdar, Presentation, 2002 San Antonio Breast Cancer Symposium

Monitoring bone mineral density in women on anastrozole

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.

ATAC trial 47-month updated safety data

Adverse events	Anastrozole (A) (n [%]) N=3092	Tamoxifen (T) (n [%]) N=3093	Relative risk A/T
Endometrial cancer	3 (0.1)	15 (0.7)	0.20
Vaginal bleeding	147 (4.8)	270 (8.7)	0.54
Vaginal discharge	94 (3.0)	378 (12.2)	0.25
Cerebrovascular events	34 (1.1)	70 (2.3)	0.49
Thromboembolic events	68 (2.2)	116 (3.8)	0.59
Hot flashes	1082 (35.0)	1246 (40.3)	0.87
Musculoskeletal disorders	936 (30.3)	732 (23.7)	1.28
Fractures	219 (7.1)	137 (4.4)	1.60

DERIVED FROM: **Sainsbury R on behalf of the ATAC Trialists' Group. Beneficial side-effect profile of anastrozole compared with tamoxifen confirmed by additional 7 months of exposure data: A safety update from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial.** *Breast Cancer Res Treat* 2002; Abstract 633.

Chemotherapy in the ATAC trial

Chemotherapy use is an unfortunate confounding variable in the ATAC trial. Those women with the greatest lymph node involvement and worst prognosis received chemotherapy. Although there are wide confidence intervals, tamoxifen and anastrozole appear equivalent in this subgroup of patients.

We argue about the reasons for this among members of the steering committee. Aman Buzdar, for example, believes that this equivalence could have resulted from the heterogeneity in chemotherapy regimens used. I believe the most likely explanation is statistical noise, because there were so few events in this subgroup of 20 percent of the whole study population. The only other explanation I can come up with is that the endocrine therapy was given after the completion of chemotherapy, not synchronously. We now know that tamoxifen performs better if delayed until after the completion of chemotherapy.

This is not a reason to withhold anastrozole in the subgroup of women receiving chemotherapy. Even in these women, anastrozole is equivalent to tamoxifen — equivalently good. Despite possible equivalence in efficacy, the tolerability and safety profile favors anastrozole.

One important issue is the reduction in gynecological symptoms with anastrozole. Aside from a decrease in endometrial cancer, there is a 50 percent reduction in the incidence of vaginal bleeding, a condition that is frightening and leads to overinvestigation and excess hysterectomies. This reason alone is an argument to use anastrozole.

Other aromatase inhibitors in the adjuvant setting

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 anti-aromatase 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.

Ongoing Phase III randomized adjuvant trials comparing aromatase inhibitors to tamoxifen

Protocol ID	Eligibility	Randomization Arms
CRC-TU-TEAM/ EU-20149	Any N; primary tumor > 3cm or grade III & > 1 cm, MO	ARM 1: Tamoxifen x 5 years ARM 2: Exemestane x 5 years
IBCSG-1-98/DAN-DBCG -IBCSG-1-98/FRE-FNELCC-IBCSG-1-98 EU-99022/IBCSG-18-98/ NOVARTIS-2026703019	pT1, pT2, pT3; pN0, pN1, pN2 or MO	ARM 1: Tamoxifen x 5 years ARM 2: Letrozole x 5 years ARM 3: Tamoxifen x 2 years → Letrozole x 3 years ARM 4: Letrozole x 2 years → Tamoxifen x 3 years

SOURCE: NCI Physician Data Query, February 2003

Follow-up of patients enrolled in the ATAC trial

After a long debate, and at the recommendation of the data-monitoring and safety committee, we agreed to close the combination arm of ATAC. We are in the process of doing this, and although it sounds simple, it isn't. We are obtaining ethical approval and going through the individual clinician investigators to unblind the patients on the combination arm. We are providing leaflets and information to help the clinicians and patients reach a decision about either stopping both drugs or continuing on one. We are not making recommendations about what should be done.

The combination arm results looked similar to tamoxifen last year, but they are beginning to look worse. There is a relative risk of 1.1 favoring tamoxifen over the combination, which is not statistically significant by any means, but it just might continue to diverge.

When the trial results became public last year, we were concerned that many patients would want to be unblinded. This would have diluted the study and resulted in a crossover. But, it has been a nonevent. We re-consented women on the monotherapy arms of the trial, and it hasn't posed a problem. Only a handful of patients asked to be unblinded.

We are not unblinding the monotherapy arms of the trial, because most women in the tamoxifen arm have been on tamoxifen for four years. We cannot recommend switching to anastrozole, because we have no idea what might happen. The monotherapy arms will remain blinded after completion of therapy to avoid bias in follow-up.

Cultural differences in interpretation of chemoprevention data

There is a cultural clash with regard to chemoprevention. The IBIS-II trial doesn't please the Americans at all, because it has a placebo arm. The study will be anastrozole against placebo, because in the United Kingdom and Australia, we do not believe tamoxifen is the standard of care. A substratum of IBIS-II will look at anastrozole versus tamoxifen in DCIS, mirroring what Richard Margolese is doing in the NSABP.

We thought that NSABP P-1 reported prematurely, and because there has been some crossover, we will learn nothing more from this trial. Jack Cusick, principal investigator of the IBIS trial, did a meta-analysis of the four tamoxifen prevention trials, which showed a significant prevention or delay of estrogen receptor-positive breast cancers, but significant adverse events from tamoxifen. The net effect on all-cause mortality is a relative risk of 1. We believe we have proof of principle of tamoxifen prevention, but cannot recommend tamoxifen, because thousands of women would be subject to the side effects of tamoxifen, including thromboembolic disease and death — to delay a few estrogen receptor-positive breast cancer events. The net health improvement is zero.

Even if the results of IBIS-II play out, I'm not sure whether anastrozole will be used for prevention. Years ago, when we embarked on the tamoxifen prevention

trial, I calculated that two percent of postmenopausal women will develop breast cancer over a 10-year period. A magic drug that prevented half of breast cancers would reduce this to one percent. We are exposing 99 out of 100 women to side effects to benefit of one woman. Unless the drug has other beneficial effects, you have a problem.

I predicted that chemoprevention in premenopausal women would have to be a contraceptive that also prevented cancer, which is not implausible. For postmenopausal woman, an ideal agent would prevent osteoporosis as well as breast cancer — thus, raloxifene is a good bet. The mistake with the STAR trial is the tamoxifen arm rather than placebo control.

IBIS-II: INTERNATIONAL BREAST CANCER INTERVENTION STUDY-2 Open Protocol

Projected Accrual: 6,000 women

Eligibility	Postmenopausal women with increased breast cancer risk

ARM 1	Anastrozole x 5 years
ARM 2	Placebo qd x 5 years

SOURCE: Jack Cuzick, PhD, Personal Communication, November 2002.

IBIS-II DCIS: INTERNATIONAL, MULTI-CENTER STUDY OF TAMOXIFEN VERSUS ANASTROZOLE WITH POSTMENOPAUSAL WOMEN WITH DUCTAL CARCINOMA IN SITU (DCIS) Open Protocol

Projected Accrual: 4,000 patients

Eligibility	Postmenopausal women, DCIS removed within last six months, ages 40-70

ARM 1	Tamoxifen qd + placebo
ARM 2	Anastrozole qd + placebo

SOURCE: Jack Cuzick, Personal Communication, November 2002.

NSABP B-35: TAMOXIFEN VERSUS ANASTROZOLE IN POSTMENOPAUSAL PATIENTS WITH DUCTAL CARCINOMA IN SITU Open Protocol

Projected Accrual: 3,000 Patients

Eligibility	Postmenopausal women with DCIS treated with lumpectomy, ER-/PR-positive or borderline

Stratification: Age (<60 versus ≥60)

ARM 1	Tamoxifen + placebo qd x 5 yrs + XRT
ARM 2	Anastrozole + placebo qd x 5 yrs + XRT

Study Contact: Richard Margolese, Chair
National Surgical Adjuvant Breast and Bowel Project
Tel: 514-342-3504

SOURCE: NCI physician Data Query, February 2003

Anastrozole in the prevention setting

Some might argue that the reduction of contralateral breast cancers in ATAC looks less promising with the updated data than with the original data — it has gone from about a 60 percent to about a 50 percent relative reduction in contralateral breast cancer in the estrogen receptor-positive group. We had the same experience early on with tamoxifen. The extremely dramatic difference seen at three years was reduced over the next few years. This suggests that these endocrine agents don't prevent cancer, but rather delay the appearance of cancer. Perhaps anastrozole delays the appearances of breast cancer for longer than tamoxifen.

I am very confident that anastrozole will reduce the risk of estrogen receptor-positive breast cancers — the adjuvant setting will predict the preventive setting. The issue to me is the trade-off and harm/benefit equation.

Trials of ovarian suppression plus aromatase inhibitors in premenopausal women

Combining ovarian ablation with aromatase inhibitors in hormone-responsive premenopausal women is a very attractive proposition. We must take our hats off to the Austrian collaborative group, which has emerged as a world leader over the last few years. Its study design is extremely elegant and rational. I will watch this beautiful study with great interest.

ANASTROZOLE OR TAMOXIFEN IN COMBINATION WITH GOSERELIN (± ZOLEDRONIC ACID) AS ADJUVANT TREATMENT FOR HORMONE RECEPTOR-POSITIVE PREMENOPAUSAL BREAST CANCER Open Protocol

Protocol ID: ABCSG-12

Eligibility	Premenopausal women with Stage I/II, ER+/PR+ breast cancer, <10 positive lymph nodes

ARM 1	Surgery ➜ goserelin + tamoxifen
ARM 2	Surgery ➜ goserelin + tamoxifen + zoledronic acid
ARM 3	Surgery ➜ goserelin + anastrozole
ARM 4	Surgery ➜ goserelin + anastrozole + zoledronic acid

DERIVED FROM: Presentation, M Gnant, San Antonio Breast Cancer Symposium 2002.

Breast conservation rates in the ATAC trial

Gershon Locker presented breast conservation rates in the ATAC trial at San Antonio. The dramatic finding is that breast conservation is much less common in the United States than in the United Kingdom and other countries. This study shows the beauty of this incredible international database, which allows us to explore cultural differences. It is fascinating that the two countries with the highest rates of breast conservation were France — which is not unexpected — and Brazil. Brazil is obsessed with the "body beautiful," but in addition, most Brazilian radiotherapists trained in France, so we see an interesting cultural issue.

In fairness to the Americans, we should not overinterpret these data. The United Kingdom is a small country in which everyone lives within 100 miles of a radiotherapy center. In contrast, parts of the United States are thousands of miles from a radiotherapy center. Radiation therapy is six weeks of treatment. I can sympathize with surgeons and women for whom it is just impractical to have breast-conserving surgery.

Intraoperative radiation therapy

This technology, in theory, could allow us to give all radiotherapy at the time of surgery with a portable machine in a community hospital. We have a neatly packaged mobile electron generator, which delivers x-rays at the tip of the probe. You can remove the tumor, apply a spherical applicator to the tumor bed cavity, wrap the tumor bed around this applicator and deliver radiotherapy to the index quadrant. The whole process adds only half an hour to the operating time.

This technique gives the biological equivalent dose of 50 Grey to the tumor bed. The geometry is better than conventional radiotherapy. Traditional conformal radiotherapy conforms to an uncertain shape. With this method, we conform the cavity to the radiotherapy source, so I think we'll do better than with conventional external beam radiation.

We did a Phase II study in 40 patients, and although I distrust Phase II studies, it appears extremely safe with excellent cosmetic results. Only one woman developed ulcerated skin, which ultimately healed. In this series, over the maximum four or five years of follow-up, we have not had a single local recurrence.

Trial of intraoperative radiation therapy

We have opened an exciting trial, randomizing patients to conventional postoperative radiotherapy versus intraoperative radiotherapy. We have a descriptive study nested within a pragmatic trial design. The pragmatic aspect is that we take all comers, providing that the tumor size relative to breast size allows us to fit an appropriate size applicator. Beyond that, we are only excluding those with lobular invasive cancer or extensive intraductal cancer. We've also allowed a descriptive entry. In other words, you can predetermine to admit only small, well-differentiated, node-negative tumors in older women.

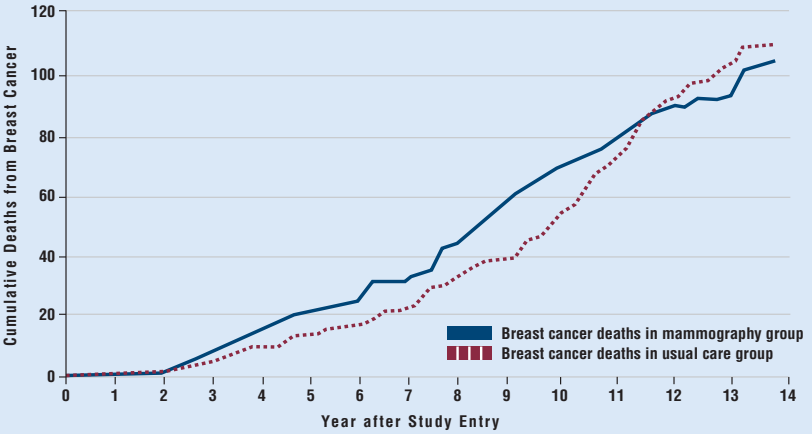
We're hoping to enroll 2,000 patients in the study, so we need to spread our wings. There is enormous interest, and we have started randomization. We have groups in Australia, North America and Germany.

Mammography in women under age 50

The latest Canadian trial results published in *Annals of Internal Medicine* in September do not demonstrate an advantage in breast cancer mortality. In fact, there is an excess mortality from breast cancer in women under 50 for the first 10 years of the study. This excess mortality in the early years has been also been noticed in the overviews of the screening trials as well.

I had a patient with screening-detected DCIS. After a biopsy, the patient was advised to have surgery, however she chose not to have treatment. She saw me six to nine months later with a breast full of cancer. That is not the natural history of DCIS, but rather the natural history of perturbed, incompletely excised DCIS. The biological mechanism is perturbation of the tumor or its environment, which induces angiogenesis.

Breast cancer deaths in women ages 40-49 with and without mammography*



***Concerns were raised about contamination because 26% of the patients in the usual care group had at least one mammography outside the study.**

REPRINTED WITH PERMISSION. Miller AB et al. **The Canadian National Breast Screening Study-1: Breast Cancer Mortality after 11 to 16 Years of Follow-up. A randomized screening trial of mammography in women age 40 to 49 years.** *Ann Intern Med* 2002;137(5):305-315. **Abstract**

Most *in situ* cancers are latent cancers, and angiogenesis is the trigger from latency to invasion. Likewise, I believe most patients with invasive cancer have metastases in dynamic equilibrium, which progress and become life threatening when the system is perturbed and angiogenesis is induced. Women with latent breast cancer or occult metastases are living close to a chaos boundary, and we perturb the system at our peril.

Informed consent for mammography in women over 50

My argument against screening women over 50 is not that it has no effect, but that we are disingenuous in the way we invite women to be screened. I passionately believe that women should make an informed choice.

With systemic therapy, we bend over backwards to inform women of the absolute benefits. We agonize whether a two or three percent improvement in five-year survival is worth the "side effects," and we counsel our patients this way.

We tell women that screening will save their lives and reduce their risk of dying by 20 percent. In absolute terms, we have to screen 1,000 women for 10 years to save one life — one in a thousand. If we told women truthfully, "If I screen you for 10 years, you will have one in a thousand less chance of breast cancer death, but a significant risk of overdiagnosis, false alarms, health insurance issues, unnecessary biopsies and detection of duct carcinoma *in situ*, which never would have troubled you," many women would refuse it.

In the United States, I think there is a profit motive, and in the United Kingdom, it's social engineering. I think it's almost fascistic to decide what is good for women and coerce them to come forward for screening without telling them the whole truth.

Select publications

Mammographic screening in women under 50 years old

16-year mortality from breast cancer in the UK Trial of Early Detection of Breast Cancer. *Lancet* 1999;353(9168):1909-14. **Abstract**

Alexander FE et al. **14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening.** *Lancet* 1999;353(9168):1903-8. **Abstract**

Andersson I, Janzon L. **Reduced breast cancer mortality in women under age 50: Updated results from the Malmo Mammographic Screening Program.** *J Natl Cancer Inst Monogr* 1997;(22):63-7. **Abstract**

Bjurstam N et al. **The Gothenburg Breast Cancer Screening Trial: Preliminary results on breast cancer mortality for women aged 39-49.** *J Natl Cancer Inst Monogr* 1997;(22):53-5. **Abstract**

Cox B. **Variation in the effectiveness of breast screening by year of follow-up.** *J Natl Cancer Inst Monogr* 1997;(22):69-72. **Abstract**

Frisell J, Lidbrink E. **The Stockholm Mammographic Screening Trial: Risks and benefits in age group 40-49 years.** *J Natl Cancer Inst Monogr* 1997;(22):49-51. **Abstract**

Kerlikowske K. **Efficacy of screening mammography among women aged 40 to 49 years and 50 to 69 years: Comparison of relative and absolute benefit.** *J Natl Cancer Inst Monogr* 1997;(22):79-86. **Abstract**

Larsson LG et al. **Updated overview of the Swedish Randomized Trials on Breast Cancer Screening with Mammography: Age group 40-49 at randomization.** *J Natl Cancer Inst Monogr* 1997;(22):57-61. **Abstract**

Miller AB et al. **The Canadian National Breast Screening Study-1: Breast Cancer Mortality after 11 to 16 Years of Follow-up. A randomized screening trial of Mammography in women age 40 to 49 years.** *Annals of Internal Medicine* 2002;137(5):305-315. **Abstract**

Morimoto T et al. **Breast cancer screening by mammography in women aged under 50 years in Japan.** *Anticancer Res* 2000;20(5C):3689-94.

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Edited comments by Dr Ravdin

ATAC trial data update

After 47 months, the disease-free survival data from the ATAC trial look very good. The curves continue to diverge, and there is no sign that they are coming together.

It's like a primary election with 80 percent of the precincts reporting, and a pretty solid lead for a candidate. It's very likely that in five years, the anastrozole arm will be superior in terms of relapse-free survival. Given its current lead, it's virtually impossible that it won't be.

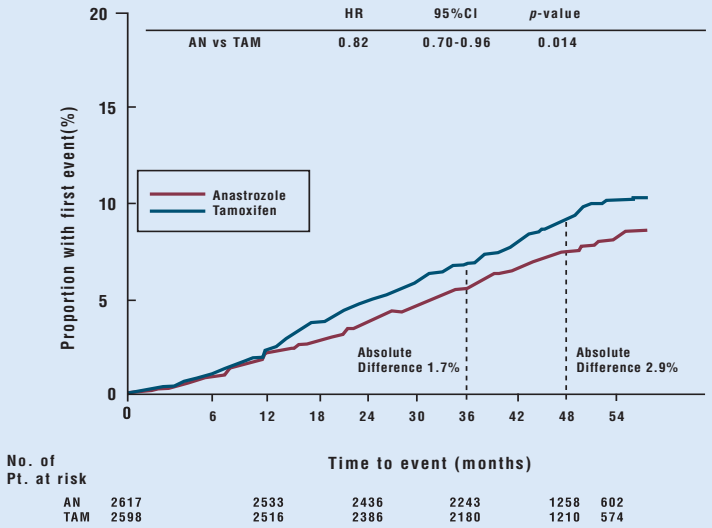
Tamoxifen only reduces mortality by about 30 percent, so there's a lot of room for improvement. At this time, no mortality data on anastrozole has been presented. It is possible that because of the kind of relapses anastrozole prevents that there won't be as great an effect on survival as on disease-free survival. However, if it has a large effect on either, it would still be considered beneficial.

ATAC trial data update: Impact on clinical care

Until now, 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. The FDA did, however, find adequate evidence to allow approval of the drug in the adjuvant setting. There is a risk with either therapy, and some patients will want the new therapy with the potential to be better.

Probability of first event in receptor-positive population



DERIVED FROM: A Buzdar, Presentation, 2002 San Antonio Breast Cancer Symposium

I'm particularly tempted to use anastrozole in patients at increased risk for a thrombotic event. I include age as a risk factor, because, for example, a 65-year-old woman has a one- to two-percent chance of a major thrombotic event over the next five years. Anastrozole would not elevate that event rate; therefore, if the patient has good bone mass, placing her on anastrozole becomes a safety issue, regardless of whether there is improved efficacy.

Anastrozole and bone loss

The updated safety data still shows that anastrozole is better in terms of thrombotic events and endometrial cancer, but worse in terms of fractures. I would like to see more mature safety data.

There is an important carryover toxicity effect that might be expected after the drugs are stopped. For example, tamoxifen has a carryover effect in endometrial cancer risk for five years after therapy. The real question with anastrozole is whether the bone loss patients experience during therapy increases their risk for the rest of their lives.

I'm not half as worried about osteoporosis as I am about thrombotic events with tamoxifen. Osteoporosis is like watching a hurricane come in from Africa — you can prepare for it, predict where it's going to hit and do something to make yourself less vulnerable to its effects. In patients I start on adjuvant anastrozole, I routinely check baseline bone mineral density to determine which patients need to be monitored soon or started on a bisphosphonate to protect bone mass.

Prevention of bone loss: Bisphosphonates

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 got zoledronate.

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

Advantages to a well-powered trial

It is heartening that the number of women in the ATAC trial was greater than the number of postmenopausal, ER-positive women who received five years of tamoxifen in the overview. I applaud the ATAC trial because it is enormously overpowered to determine which drug is better. The beauty of a trial being overpowered is that you can begin to ask subset questions — that's the power of the overview.

I also like overpowered trials because they are almost impossible to replicate. For example, ATAC may be the only chance to ask what predicts for benefit with tamoxifen or anastrozole, because if survival and toxicity advantages emerge for the anastrozole arm, it may be impossible to do such a trial again and ask the biological questions as corollaries to it. To do it all in one 9,000-patient study is immensely powerful. This trial will never be replicated.

Use of other aromatase inhibitors in the adjuvant setting

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 both better and 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.

Calculating expected benefit from therapy

The informal way to calculate a patient's expected benefit is to multiply her risk of recurrence by the relative risk reduction expected from a therapy. For example, if a patient has a 60 percent risk of recurrence and your therapy reduces that by 40 percent, multiplying those two percentages together gives a 24 percent benefit.

This is a rough approximation, and it doesn't quite work that way. In reality, the 40 percent reduction is not a 40 percent composite reduction, but rather a 40 percent reduction that occurs in each year. It compounds like interest in a bank account and actually ends up giving less of an effect than you would expect.

The reason is mathematical, not biological. On a curved surface, you can't lay your ruler down across the entire curve. Rather, the ruler is essentially touching the curve at any given point and telling you what the slope is at that point. That's what the hazard is — it tells you what the actual ratios of the slopes would be if you put the ruler at four years on both curves.

I wrote a program on adjuvant therapy that shows how the numerical method for calculating benefit works. It's accessible online at **www.adjuvantonline.com**.

Small reductions may offer big benefits

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

I would not expect any therapy to be effective in 100 percent of patients because breast cancer is a very heterogeneous disease. Patients can have ER-positive and -negative disease or HER2-positive and -negative disease. Different cancers express different genes and, therefore, have potentially different vulnerabilities to therapy. I would be amazed if any single therapy was effective in more than 50 percent of patients. Given that, when you see a 20 percent effect, an additional two percent represents perhaps 20 percent of that overall population, which is significant. And perhaps that particular agent benefits 20 percent of the patients who aren't benefiting from other strategies.

I believe the conquest of breast cancer is not going to be one magic bullet, but rather identifying sets of patients whose cancers have specific vulnerabilities. Maybe none of those sets will be greater than 20 percent of the total, so even the greatest therapies may be very effective only for a small set of patients.

Impact of therapy on early versus late relapses

The divergence of curves with effective adjuvant therapy has not been adequately studied, and I think there is an enormous hidden story there. Some curves begin to diverge within the first year, continue to diverge for the first five years and then parallel each other. Curves like this tell me the therapy is killing the rapidly progressive, early relapsing clones.

The last overview showed that the proportional benefits for chemotherapy emerged entirely because of impact on relapses within the first five years. There was no impact at all on relapse from the average chemotherapy after five years — a fascinating result.

With chemotherapy, we are not yet touching the late, slowly proliferating population, which accounts for perhaps one-third of all relapses, particularly in ER-positive disease. This is where vaccines may be of particular benefit.

In contrast, there was a curve for a particular therapy presented at San Antonio that showed no difference in the first five years, but the advantage accumulated in the second five years. The curve suggested the therapy showed no advantage against the rapidly progressive clones in the early relapsers, but that the advantage emerged in the late relapsers.

Hormone therapy is more balanced than chemotherapy in the impact on the second five years. In NSABP P-1 and B-14, the curves actually slightly diverge. The therapy is probably acting on the slower and stalled clones. This has not been adequately studied, and I think it's worth some additional research

CALGB 9741 results and the impact on clinical care

I think the results of CALBG 9741 will pressure physicians to introduce the dose-dense regimen. Many clinicians will want to obtain some experience with dose density in their very high-risk patients, who might have received very high-dose chemotherapy with stem-cell support in the past. For those patients, these new dose-dense regimens are extremely interesting.

The problem is that clinicians will want more information about the toxicity profile. There was evidence that the sequential, noncombination dose-dense regimen was less toxic. Many of us are leery about giving very large cumulative doses of doxorubicin, so this will take some soul searching. I don't think physicians are going to suddenly adopt one of the dose-dense regimens tomorrow morning; rather, I think they will ease into it.

Palliation versus cure for metastatic disease

Physicians generally agree that the targets of treatment for patients with metastatic disease are long-term health maintenance and disease palliation. Today, we don't talk about intensive therapy for cure. At San Antonio five years ago, there would have been discussions about high-dose chemotherapy

with stem-cell support. Now we discuss the breadth of single agents available to support patients. We're looking to maintain patients' function for prolonged periods, rather than to induce cure.

Physician acceptance of capecitabine

Kathy Miller presented a case at a seminar recently in which the patient progressed shortly after receiving adjuvant ACT. When the members of the audience were asked what agent they would use next, the most common answer was capecitabine alone. I was a surprised by that because the acceptance of capecitabine was slow in the beginning.

I attribute this slow acceptance to two factors. First, capecitabine was approved at too high a dose; so many physicians had an unfavorable first experience using it. Second, capecitabine is the first drug I can think of that was approved before there were any publications in the literature.

Physician acceptance has grown as lower doses have been tried and patients' tolerance has improved. In addition, articles have suggested a relatively high response rate with capecitabine as first-line therapy and in combination therapy, particularly with docetaxel.

Capecitabine/docetaxel combination in the adjuvant and metastatic settings

The capecitabine/docetaxel study was important because a very large number of patients consider combination adjuvant therapy. Therefore, the most valuable outcome of this trial in the metastatic setting was learning whether or not this combination might have promise in adjuvant therapy.

Patients with metastatic disease in really desperate situations might have a high response rate with the combination, but that's not the majority of patients. Most patients don't relapse, and those who do don't usually find themselves in a desperate situation early on.

If there had been a sequential arm of capecitabine followed by docetaxel, I don't think we would have seen a great deal of difference between the two arms, as in many other crossover studies.

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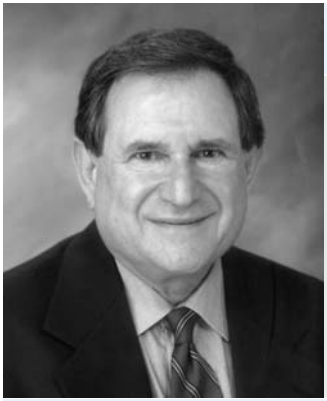

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Edited comments by Dr Vogel

Rationale for the design of the trastuzumab monotherapy trial in metastatic disease

It became readily apparent to me early on that there was a subset of women with metastatic HER2-positive disease who really did not want to receive chemotherapy up front, so I lobbied for having a first-line, single-agent trastuzumab trial. Many other investigators — including Melody Cobleigh and Debu Tripathy — were also very instrumental in moving this concept forward. So, this was really the third major initial trial to look at what trastuzumab could do in metastatic breast cancer. All of these were basically proof-of-principle trials. While everybody was entering into these trials with some degree of optimism, it wasn't a "slam dunk" that trastuzumab was really going to provide an important benefit.

Our trial was a Phase II, single-arm study, and we accrued 114 patients. The patients were quite gratified because they were treated with a relatively nontoxic form of therapy, at least from the standpoint of subjective toxicities.

Results of the trastuzumab monotherapy trial

The overall, published response rate for all the IHC 2+/3+ HER2-positive patients was 26 percent. We've subsequently learned that there is a very high false-positive rate for the IHC 2+ patients. Consequently, further analyses were done using only the IHC 3+ patients, and ultimately, the FISH-positive patients.

Another interesting outcome measurement is prolonged stable disease, because it seemed that patients were responding to trastuzumab more like they would to hormonal therapy rather than to chemotherapy. We were seeing prolonged periods of disease stabilization, even though we weren't able to objectively record definitive responses, as classically defined. So, we also evaluated the group of patients with prolonged stable disease for greater than six months.

If you look at the group of patients who were FISH-positive, and if you add the patients with prolonged stable disease to those who had objective responses, about half the patients responded to first-line, single-agent trastuzumab.

According to strict statistical guidelines, we observed a median duration of response of 18 months. That is far in excess of what was seen in the pivotal trial, and it could very well be that a patient here or there could have skewed that result.

Efficacy of first-line trastuzumab in HER2-overexpressing metastatic breast cancer

Subset	Objective Response	Clinical Benefit*
All assessable patients (n=111) [95% CI]	26%	38%
Trastuzumab		
2 mg/kg weekly (n=58) [95% CI]	24%	34%
4 mg/kg weekly (n=53) [95% CI]	28%	42%
Estrogen receptor		
positive (n=52)	23%	36%
negative (n=54)	30%	39%
HER2		
IHC 3+ (n=84)	35%	48%
IHC 2+ (n=27)	0%	7%
FISH		
positive (n=79)	34%	48%
negative (n=29)	7%	10%
Previous adjuvant doxorubicin (n=57)	32%	41%

*Clinical Benefit = complete, partial or minor response or stable disease > 6 months

DERIVED FROM: Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20:719-726. Abstract

Management of patients with HER2-positive metastatic disease

There remains considerable controversy 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 American College of Pathology does something to iron out this problem of quality control, I continue to use FISH.

There is a significant survival benefit for the combination of trastuzumab plus chemotherapy versus chemotherapy alone. For that reason and because some of the patients might wish to avoid cytotoxic chemotherapy at that point in time, it behooves us to move in the direction of ascertaining HER2 status prior to initiation of first-line chemotherapy.

I use single-agent trastuzumab in a similar manner as hormonal therapy. There are subsets of women with HER2-positive disease who don't have horribly aggressive metastatic breast cancer. In those relatively asymptomatic patients who do not have visceral crisis or rapidly progressive disease and are not incapacitated by symptoms, I have no problem at all starting them on first-line, single-agent trastuzumab. However, the patients must be fully informed that they may be giving away something in terms of response rate, based on an analysis of cross-trial comparisons with the combination regimens.

Management of the patient with ER-positive, HER2-positive metastatic breast cancer

Although it's controversial, some physicians use the combination of trastuzumab and hormonal therapy off-protocol for HER2-positive, hormone receptor-positive patients. I don't use that combination. Hormonal therapy is the mainstay of treatment and can produce prolonged responses. It's very important to know whether a patient has hormone-sensitive disease. I would not like to cloud the issue by adding trastuzumab until such time as the ongoing clinical trials are published and indicate a definite advantage for the combination versus the sequential approach.

There's a worldwide trial that has been accruing very, very slowly that compares anastrozole with or without trastuzumab. Everybody underestimated the difficulty that would ensue with this particular type of protocol. Approximately 20 percent of tumors will be FISH-positive, and of those, perhaps 40 percent will be ER-positive. Now you're already down to less than 10 percent of the overall breast cancer population. The eligibility criteria carve away another few percent. And so you're down to probably about seven percent of the overall patient population who could potentially be eligible for such trials. It's not at all surprising that there is difficulty accruing to these types of trials.

PHASE II/III RANDOMIZED STUDY OF ANASTROZOLE WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN) IN POSTMENOPAUSAL WOMEN WITH HORMONE-RECEPTOR POSITIVE HER2-OVEREXPRESSING METASTATIC BREAST CANCER Open Protocol

Protocol IDs: ROCHE-BO16216, CWRU-030118, GENENTECH-H2223g, ROCHE-1100, ROCHE-B016216E

Eligibility	Postmenopausal women with ER- and/or PR-positive, HER2-positive (IHC 3+ or FISH-positive) metastatic breast cancer

ARM 1	Anastrozole qd + trastuzumab qw
ARM 2	Anastrozole qd

In both arms, treatment continues for at least 2 years in the absence of disease progression or unacceptable toxicity. Patients in either arm who do not develop disease progression may continue receiving treatment, in the arm to which they were originally randomized, during the extension phase of this study. Patients in Arm 2 who develop disease progression may receive treatment in Arm 1 during the extension phase in the absence of further disease progression.

Study Contact: Bernd Langer, PhD, Protocol chair
Ph:41-61-68-80638

SOURCE: NCI Physician Data Query, February 2003

A palliative approach to women with HER2-positive metastatic disease

Until we are able to break the "cure barrier" of metastatic breast cancer, the major philosophical goal is palliation. I don't necessarily know that anthracyclines, or even taxanes, are the best chemotherapeutic agents for palliation of metastatic breast cancer.

In this day and age, patients are frequently treated with an anthracycline plus docetaxel as first-line treatment in metastatic breast cancer. That's counter to my own personal philosophy of the management of metastatic breast cancer.

An anthracycline/docetaxel combination is a very reasonable combination for a patient with visceral crisis. However, the vast majority of patients don't present with visceral crisis. Consequently, if I had a patient who was HER2-positive, I would want to "put my best foot forward" from the standpoint of toxicity.

I might consider, as a first choice, vinorelbine plus trastuzumab. The weekly taxanes combined with trastuzumab are also reasonably good options. And here, I would probably choose paclitaxel over docetaxel, because even with weekly docetaxel, we run into problems with the epiphora. And we still have the fluid-retention problem with docetaxel, more so now with the weekly than even the every-three-week schedule.

On the other hand, we now have new data, both from the pilot trials of the BCIRG and also from the study just presented at San Antonio by Nick Robert for the US Oncology group, on the use of carboplatin plus paclitaxel and trastuzumab. The duration of response in those trials appears to be, in cross-trial comparisons, superior to those seen with trastuzumab in combination with vinorelbine, paclitaxel or docetaxel.

We use that combination in our practice and are actually studying that in the neoadjuvant setting. If I had a patient with visceral crisis who was HER2-positive, I would strongly consider using a combination of carboplatin, probably with docetaxel and trastuzumab.

Treating the patient with ER-negative, HER2-negative metastatic breast cancer

The patient with hormone receptor-negative, HER2-negative de novo metastatic disease constitutes a major dilemma. Sometimes these patients have really minimal disease.

Whenever possible, I like to try to observe these patients, as opposed to starting cytotoxic chemotherapy, because I'm really not convinced that the early institution of cytotoxic chemotherapy is going to lead to a survival advantage. It is likely to impact negatively on quality of life. On the other hand, the vast majority of women, once they know they have metastatic disease, are not going to accept the concept of observation.

My next step would be to try to find a nontoxic clinical trial that I could enter the patient on — the new targeted therapies or the biologics. When it comes to cytotoxic chemotherapy, my choice would not necessarily be an anthracycline and probably not even a taxane.

I'm impressed with the tolerability of and response to single-agent therapy with capecitabine, vinorelbine, liposomal doxorubicin or gemcitabine. CMF is also a well-tolerated regimen. Another regimen that we use is a combination of mitoxantrone, 5-FU and leucovorin, where the 5-FU and leucovorin are given on days one and eight and then mitoxantrone on day one. This regimen is not utilized by very many people, but you can obtain very nice responses with minimal toxicity.

Several questions arise. How do you choose among all of these different options? Do you choose a combination? Do you choose sequential single agents? Unless the patient is part of a clinical trial where we're trying to find such significant activity for a combination that it could be moved into the adjuvant setting, I would probably use sequential single agents.

Vinorelbine/capecitabine (VINOCAP) for patients with ER-negative, HER2-negative metastatic disease

For patients where you might need a little bit more "bang for your buck," I consider a combination of vinorelbine and capecitabine, where we've seen excellent responses. There are at least six Phase II trials — all of them concordant — showing excellent response rates with good tolerability for that particular combination.

Our group now has about 24 patients in an observational study evaluating the combination of vinorelbine and capecitabine. There were some patients receiving up to fourth-line chemotherapy. We found that the overall response rate was about 56 percent, which was quite credible. Toxicity was minimal at what might be considered virtually homeopathic doses of both of the drugs.

The median dose intensity for vinorelbine was about 18 mg/m^2 per week, whereas the standard dose is either 25 or 30 mg/m^2 per week. In reality, whatever study you look at — because of the myelotoxicity — the median dose intensity is usually about 21 to 22 mg/m^2 per week.

In our particular series, the dose intensity was actually even lower. With regard to the dose intensity of capecitabine, all of our patients were treated with a median dose intensity of about 1,500 mg/m^2 per day. So, we're talking about relatively low doses of these two agents.

VINOCAP: Toxicity profile

There's very little alopecia associated with the vinorelbine/capecitabine combination. One disadvantage is that we don't give — in our particular practice setting — vinorelbine without a portacath. Many people do, both in the United States and abroad, but every once in a while you see a patient with a

significant arm-pain syndrome. And when you've had one or two patients with this, you really do not want to repeat it. You very seldom see a paralytic ileus with vinorelbine, but certainly, when this occurs, you start to become "gun shy," because it's a very serious complication.

The major side effect of this combination is neutropenia from the vinorelbine, and, as long as the doses are low enough from the capecitabine, you really should see very little diarrhea, mucositis or hand-foot syndrome.

Phase II clinical trials of vinorelbine and capecitabine (VINOCAP) reported in patients with metastatic breast cancer

Study	# patients	Doses VINO/CAP	Objective Response CR + PR	SD	Grade III/IV neutropenia	Grade III/IV hand-foot
[1]Ahn Sr, JH et al., 2002	19	25 mg/m^2 2,500 mg/m^2	53%	NR	22%	0%
[2]Ghosn M et al., 2002	23	25 mg/m^2 1,650 mg/m^2	61%	13%	13%	17%
[3]Hess DD et al., 2002*	36	20-25 mg/m^2 800-1,250 mg/m^2	50%	28%	NR	0%
[4]Domenech al., 2001	12	18 mg/m^2 2,000 mg/m^2	58%	25%	25%	NR

* Phase I/II dose finding study
VINO = vinorelbine; CAP = capecitabine
SD = stable disease > 6 months; NR = not reported

DERIVED FROM:

[1]Ahn Sr, JH et al. *Proc ASCO* 2002; Abstract 2030.
[2]Ghosn M et al. *Proc ASCO* 2002; Abstract 1978.
[3]Hess DD et al. *Proc ASCO* 2002; Abstract 2915.
[4]Domenech G et al. *Proc ASCO* 2001; Abstract 1939.

Nonprotocol adjuvant decision-making in the patient with ER-negative, HER2-negative, node-positive breast cancer

The presentation in San Antonio of the dose-dense chemotherapy study by Mark Citron on behalf of the Intergroup was fascinating and provides vindication for the mathematic modeling that Dr Norton and his group have been espousing over the years. I know that many of the cooperative groups around the world will want to use this to generate hypotheses. We have other regimens that also look quite good. The combination of docetaxel, doxorubicin and cyclophosphamide, or TAC, appears to provide results that are very similar to the dose-dense results of the Intergroup. So, what do you do? Do you just abandon the TAC regimen and adopt dose-dense therapy on the basis of one clinical trial? I wouldn't be prepared to do that just yet.

And then the question is: Could you do even better with dose density if you used a different taxane? Unfortunately, we still don't have good head-to-head

comparisons among the taxanes, and we're still waiting for the major pivotal trial of the Intergroup, which is AC followed by either docetaxel or paclitaxel, with both of those drugs given either every three weeks or weekly. That is a major study that will impact yet further on taxane usage. In addition, there are 56,000 women worldwide who are entered into adjuvant taxane trials. Over the next two to three years, those trials will mature and we'll know a lot better what to do with the taxanes.

Outside of the context of a clinical trial, I would give patients three options. I would tell them they could take AC followed by docetaxel, TAC or now — with the new data presented at San Antonio — I might present the possibility of using a sequential single-agent dose-dense chemotherapy regimen. However, I would make a leap of faith and substitute docetaxel for paclitaxel. I can't assure patients that sequential single-agent, dose-dense therapy is going to be the best option, but on the basis of cross-trial comparisons, it looks like it's not too dissimilar from the results one can obtain with TAC.

Comparison of adjuvant clinical trial results in patients with node-positive breast cancer: BCIRG-001 (TAC vs FAC) and CALGB-9741 (Dose-dense [DD] vs Conventional Scheduling [CS] chemotherapy)

	BCIRG-001*		CALGB-9741**	
# patients	1,491		1,973	
Median follow-up	33 months		36 months	
	Relative Reduction TAC/FAC	% Reduction	Relative Reduction DD/CS	% Reduction
Disease-free survival	RR = 0.68 p = 0.0011	32%	RR = 0.74 p = 0.007	26%
Overall survival	RR = 0.76 p = 0.11	24%	RR = 0.69 p = 0.014	31%

DERIVED FROM:* Nabholtz JM et al. **Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer (BC) patients: Interim analysis of the BCIRG 001 study. *Proc ASCO* 2002; Abstract 141.

***DERIVED FROM:* Citron M et al. **Superiority of dose-dense (DD) over conventional scheduling (CS) and equivalence of sequential (SC) vs. combination adjuvant chemotherapy (CC) for node-positive breast cancer (CALBG 9741, INT C9741).** *Breast Cancer Res Treat* 2002; Abstract 15.

Adjuvant therapy for patients with ER-positive breast cancer

After the ATAC trial results were initially presented, I began speaking with my patients about the results. I told them that the data were still early, and we discussed the risk-benefit profile and quality-of-life issues. Then they made the decision to receive anastrozole or tamoxifen.

There are some women who are so concerned about the potential for osteoporosis with anastrozole, or those who already are suffering from arthritic symptoms, that they will say, "If those side effects are predominant with anastrozole, then I'd prefer to go with tamoxifen." On the other hand, women who are deathly afraid of the uterine cancer risk and blood clots may choose to go with tamoxifen. At the moment, both of these are still very viable options.

Integrating fulvestrant into the management of patients with ER-positive metastatic disease

We treated 21 patients in the compassionate-use trial and subsequently another 14 patients after fulvestrant became commercially available. Tolerability is no problem and is comparable to the aromatase inhibitors. Patients also deal quite well with the intramuscular injection.

I really don't know where fulvestrant will "shake out" over time. We know that fulvestrant is at least as efficacious as the aromatase inhibitors. It will be very nice if fulvestrant does have the very prolonged duration of disease control, as initially published.

Select publications

Trastuzumab: 2002 San Antonio Breast Cancer Symposium update

Carey LA et al. **Response to trastuzumab (Herceptin) given with paclitaxel (taxol, T) immediately following 4AC as initial therapy for primary breast cancer (BrCa)**. *Breast Cancer Res Treat* 2002; **Abstract 424.**

Chan A et al. **Clinical efficacy & toxicity of Herceptin in metastatic breast cancer patients with tumours that overexpress Her-2 neu: The Australian expanded access program.** *Breast Cancer Res Treat* 2002; **Abstract 444**.

Chan A et al. **Multinational phase II study of navelbine (N) and herceptin (H) as first-line therapy for HER2-overexpressing metastatic breast cancer (HER2+ MBC).** *Breast Cancer Res Treat* 2002; **Abstract 434**.

Dieras V et al. **Previous cumulative anthracycline dose is the main determinant of LVEF decrease in breast cancer patients treated with trastuzumab (Herceptin®): Results of a French compassionate use program.** *Breast Cancer Res Treat* 2002; **Abstract 425.**

Filipovich E et al. **Chemotherapy with trastuzumab plus vinorelbine in patients with erb-B2 overexpressed tumor is active in metastatic breast cancer.** *Breast Cancer Res Treat* 2002; **Abstract 436.**

Gelmon K et al. **Efficacy and safety of Herceptin in women with Her2-positive (HER2+) metastatic breast cancer (MBC) who have progressed on a prior herceptin-containing regimen.** *Breast Cancer Res Treat* 2002; **Abstract 440.**

Janku F et al. **Weekly trastuzumab (T) and paclitaxel (P) in metastatic breast cancer (MBC). The impact of taxane free interval (TFI) on treatment outcomes.** *Breast Cancer Res Treat* 2002; **Abstract 435**.

Lüftner DI et al. **Evaluation of serum HER-2/neu for outcome assessment and monitoring of Herceptin plus combination chemotherapy in metastatic breast cancer.** *Breast Cancer Res Treat* 2002; **Abstract 427.**

Lüftner DI et al. **Longitudinal HER-2/neu measurements during treatment with Herceptin, epirubicin plus cyclophosphamide (HEC): Interim serum results of a phase II study in patients with**

metastatic breast cancer. *Breast Cancer Res Treat* 2002; **Abstract 423.**

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Pichon MF et al. **Serum HER-2/neu extracellular domain parallels responses to trastuzumab treatment of recurrent breast cancer.** *Breast Cancer Res Treat* 2002; **Abstract 426**.

Raab G et al. **Multicenter randomized phase II study of docetaxel (Doc) given q3w vs q1w plus trastuzumab (Tra) as first line therapy for HER2 overexpressing adjuvant anthracyclin pretreated metastatic breast cancer (MBC).** *Breast Cancer Res Treat* 2002; **Abstract 443.**

Robert N et al. **Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive advanced breast cancer.** *Breast Cancer Res Treat* 2002; **Abstract 35.**

Thomssen CH et al. **Cardiac safety of epirubicin/cyclophosphamide (EC) alone and in combination with herceptin in women with metastatic breast cancer (MBC).** *Breast Cancer Res Treat* 2002; **Abstract 430.**

Van Pelt AE et al. **Phase II study of neoadjuvant trastuzumab plus docetaxel for locally advanced and metastatic breast cancer that overexpresses HER2/neu: A preliminary report.** *Breast Cancer Res Treat* 2002; **Abstract 441.**

Yardley DA et al. **Final results of the Minnie Pearl Cancer Research Network first-line trial of weekly paclitaxel/carboplatin/trastuzumab in metastatic breast cancer.** *Breast Cancer Res Treat* 2002; **Abstract 439.**

Clinical trials involving the combination of vinorelbine and capecitabine

Ahn Sr, JH et al. **Phase II study of combination chemotherapy of capecitabine and vinorelbine in metastatic breast cancer with previous exposure to anthracycline and taxane: Preliminary results.** *Proc ASCO* 2002; **Abstract 2030.**

Domenech G et al. **Vinorelbine/capecitabine (VINOCAP) combination remission induction therapy for metastatic breast cancer (MBC).** *Proc ASCO* 2001; **Abstract 1939.**

Ghosn M et al. **Vinorelbine (Navelbine) IV and capecitabine (vinocap) as front line chemotherapy in metastatic breast cancer (MBC)**. *Proc ASCO* 2002; **Abstract 1978.**

Hess DD et al. **Phase I-II trial of capecitabine and vinorelbine in elderly patients (pts: > 65y) with metastatic breast cancer (MBC): SAKK 25/99 for the Swiss Group of Clinical Cancer Research, Berne, Switzerland.** *Proc ASCO* 2002; **Abstract 2915.**

Schott AF et al. **Vinorelbine (VR) and capecitabine (CAP) in metastatic breast cancer: Phase I/II study with correlative genotype, phenotype, and pharmacokinetics.** *Breast Cancer Res Treat* 2002; **Abstract 338.**

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Welt A et al. **Extended phase I study of capecitabine in combination with vinorelbine in pretreated patients with metastatic breast cancer.** *Breast Cancer Res Treat* 2002; **Abstract 336.**

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Edited comments by Dr Citron

Evolution of eligibility criteria for CALGB 9741 trial

As a clinical oncologist and investigator, I wanted the eligibility criteria to reflect the average breast cancer patient being treated by an oncologist with adjuvant chemotherapy. I also wanted to make it as easy as possible for oncologists to enroll patients.

The decision to accept a low baseline granulocyte count was very important. For years in the treatment of testicular cancer, we would not delay treatment because of a low count, when the goal of therapy was cure. It made sense to apply this policy to adjuvant therapy in node-positive breast cancer as well.

In addition, we wanted to increase participation by African-Americans, and benign neutropenia occurs in approximately 10 percent of this population. We didn't want to exclude them. We also wanted the arms to be balanced to prevent dose interruption and allow full-dose therapy. The easiest way to achieve that was to allow a low absolute neutrophil count (ANC) of 1,000.

Trial design and rationale for dose selection

We treated approximately 2,000 patients between four arms. The drug sequence varied in each arm, but the drugs used and the dosages were identical.

When this trial was designed in 1996, questions were raised about the optimal doses and schedules for each of the drugs. NSABP B-22 had just shown no benefit to dose escalation of cyclophosphamide, and CALGB 9344 was testing a higher dose of doxorubicin, so at that point we thought it best to go with the standard dose. There was also a lot of discussion about whether paclitaxel should be given as a 24- or a three-hour infusion. But, it was important to design the trial for outpatients. In addition, preliminary

evidence from the Gynecologic Oncology Group's trial in second-line ovarian cancer showed that those two types of infusion were equivalent. The doses were pretty much derived from standard medical practice.

PHASE III RANDOMIZED STUDY OF SEQUENTIAL CHEMOTHERAPY USING DOXORUBICIN, PACLITAXEL, AND CYCLOPHOSPHAMIDE OR CONCURRENT DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL AT 14- AND 21-DAY INTERVALS IN WOMEN WITH NODE-POSITIVE STAGE II OR IIIA BREAST CANCER
Closed Protocol

Protocol IDs: CLB-9741, E-C9741, NCCTG-C9741, SWOG-C9741

Projected Accrual: 2,000 patients

ARM I	A q 3 wk x 4 ➔ T q 3 wk x 4 ➔ C q 3 wk x 4
ARM II	A q 2 wk x 4 ➔ T q 2 wk x 4 ➔ C q 2 wk x 4*
ARM III	AC q 3 wk x 4 ➔ T q 3 wk x 4
ARM IV	AC q 2 wk x 4 ➔ T q 2 wk x 4*

*Filgrastim (G-CSF) is administered on days 3-10 after each dose of doxorubicin, paclitaxel, and cyclophosphamide.

A=doxorubicin; T=paclitaxel; C=cyclophosphamide

SOURCE: NCI Physician Data Query, February 2002 and adapted from presentation, M Citron, San Antonio Breast Cancer Symposium 2002.

Efficacy of dose-dense chemotherapy

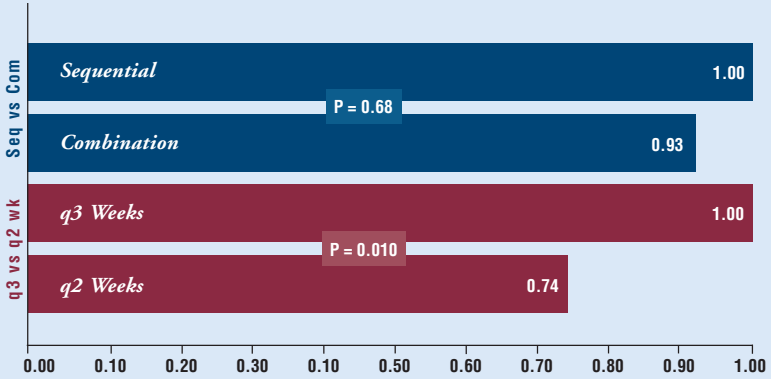
The trial had a two-by-two factorial design, and the results presented at San Antonio compared the two dose-dense arms to the two sequential arms. One disadvantage of the two-by-two analysis is that it precludes pair-wise comparison of the two dose-dense arms. We will present all four arms in the manuscript, but 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 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.

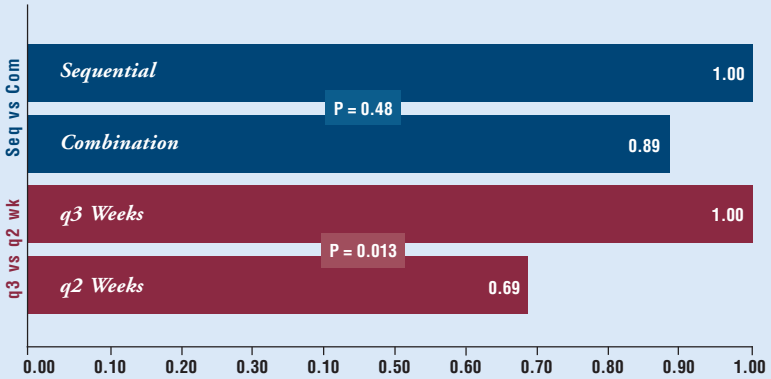
Most patients received the optimal doses of their drugs in all arms, which may be related to the low ANC requirement and the fact that less than eight percent of treatment cycles were delayed. This assured us that the benefits of dose-density could not be attributed to a lower dose or further dose delays in the conventional regimens — the arms were balanced in that regard.

Multivariate Cox Proportional Hazard Model: DFS (n=1892)



DERIVED FROM: ML Citron, Presentation, 2002 San Antonio Breast Cancer Symposium.

Multivariate Cox Proportional Hazard Model: OS (n=1892)



DERIVED FROM: ML Citron, Presentation, 2002 San Antonio Breast Cancer Symposium.

Toxicity of dose-dense chemotherapy

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 concurrent, 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 in those patients, which I had previously attributed to dexamethasone. I'm watching it more carefully now.

Toxicities observed in CALGB 9741 adjuvant clinical trial of dose-dense versus conventionally scheduled chemotherapy

	1 Sequential q3w	2 Sequential q2w	3 Concurrent q3w	4 Concurrent q2w
# treated	488	493	501	495
# studied for toxicity	99	96	101	101
Granulocytes < 0.5/ul	24%	3%	43%	9%
Febrile neutropenia hospitalized	3%	2%	5%	2%
Red cell transfusion	0%	2%	3%	13%
Neurologic: Severe sensory loss or motor weakness	1.9%	1.9%	3.9%	4.5%

DERIVED FROM: ML Citron, Presentation, San Antonio Breast Cancer Symposium, 2002.

Effect of hormone receptor status on impact of dose-dense chemotherapy

Because of the controversy regarding hormone responsiveness and paclitaxel, there was concern that hormone receptor status would affect responsiveness to therapy in this trial. However, there was no significant difference based on receptor status with dose-dense therapy. We did not plan this analysis, but because of the controversy, we looked at that subset in retrospect. There was a 19 percent reduction in patients with ER-positive disease and a 32 percent reduction in patients with ER-negative disease. There was really no difference — it works in both subsets.

A number of oncologists will not use ACT in ER-positive patients, but I think dose-dense therapy can be applied to both ER-positive and ER-negative patients with node-positive disease. I want further follow-up from the study before I start using dose density in some of the node-negative patients — generally I'm treating them with an every-three-week regimen at this point. In lower-risk patients with node-negative disease, I generally give AC times four.

Areas of future research in dose-dense therapy

We still need to verify the effect of dose-dense therapy, because the two-by-two design doesn't allow us to look at the individual arms with sufficient power. We need another large trial that's not diluted by the two-by-two effect to determine the magnitude of the difference between dose-dense and conventional dosing. We also need to refine the four arms to prove which has the highest cure rate. That would be my next step.

There are a number of other ways to study dose density. The fact that sequential versus combination therapy appears to be equivalent opens up the feasibility of studying a number of therapies sequentially — chemotherapy, monotherapy and biological therapies — in a potentially curative manner. We didn't do a quality-of-life companion in this trial, but based on my experience, it stands to reason that one drug is less toxic than two, and that sequential therapy will probably be better tolerated in the older age group. This needs to be studied because the ability to give full-dose chemotherapy in the elderly is important.

Another issue to consider is further decreasing the dose-dense interval, so that you treat again as soon as the monocytes recover. It's a little more difficult to consider this in the AC arms, because AC may cause esophagitis and other problems that may be more difficult to manage if associated with neutropenia.

Acceptance of dose density in clinical practice

Dose-dense therapy is definitely a therapeutic option for high-risk patients with breast cancer at this time. It is not the standard of care, but 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 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. I was initially embargoed from revealing the results of CALGB 9741, but now I discuss it with patients. I give them my take on the literature and my recommendation.

Most oncologists like to see five-years of follow-up in an adjuvant study. I find when I talk to physicians about emerging trends, you 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 how positively dose-dense therapy has been received. As I talk to physicians, I find they are often already using or at least considering it. This approach appears to be more widely accepted than I had expected at this time.

Personal reflections on oncology research and practice

I love oncology — I have a great practice, terrific patients, and a great staff. I enjoy my work. I am tired at the end of the day, like everyone else, but I almost always feel good about it. And I love research. Preparing the paper for CALGB 9741 has been a very interesting experience for me, and I've been totally immersed in it for about six months. I enjoy chess and, like chess, research is an enjoyable, intellectual challenge. For years, I worked in a laboratory studying DNA repair, and I always found it interesting to study basic mechanisms and then design clinical experiments.

Select publications

Clinical trials of dose-dense chemotherapy

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Citron M et al. **Superiority of dose-dense (DD) over conventional scheduling (CS) and equivalence of sequential (SC) vs. combination adjuvant chemotherapy (CC) for node-positive breast cancer (CALGB 9741, INT C9741).** *Breast Cancer Res Treat* 2002; **Abstract 15.**

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Lalisang RI et al. **Dose-dense epirubicin and paclitaxel with G-CSF: A study of decreasing intervals in metastatic breast cancer.** *Br J Cancer* 2000;82(12):1914-9. **Abstract**

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Nistico C et al. **Phase II study of epirubicin and vinorelbine with granulocyte colony-stimulating factor: A high-activity, dose-dense weekly regimen for advanced breast cancer.** *Ann Oncol* 1999 Aug;10(8):937-42. **Abstract**

Nistico C et al. **Weekly schedule of vinorelbine in pretreated breast cancer patients.** *Breast Cancer Res Treat* 2000;59(3):223-9. **Abstract**

Paciucci PA et al. **Neo-adjuvant therapy with dose-dense docetaxel (DTX) plus short-term G-CSF support for locally advanced breast cancer (LABC).** *Proc ASCO* 2002; **Abstract 1943.**

Razis E et al. **Dose-dense sequential chemotherapy with epirubicin and paclitaxel in advanced breast cancer.** *Cancer Invest* 2001;19(2):137-44. **Abstract**

Rodriguez CA et al. **Dose-dense docetaxel and mitoxantrone as first line chemotherapy for metastatic breast cancer (MBC).** *Proc ASCO* 2002; **Abstract 1938.**

Sanchez-Rovira P et al. **Biweekly gemcitabine, doxorubicin, and paclitaxel as first-line treatment in metastatic breast cancer. Final results from a phase II trial.** *Oncology (Huntingt)* 2001;15(2Suppl3):44-7. **Abstract**

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Post-test

02-1125-ES-12 BCU2 | 2003

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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

Signature: _____

Questions *(please circle answer)*:

1. VINOCAP is an abbreviation for which of the following:
a. Vincristine and capecitabine
b. Vinblastine and capecitabine
c. Vinorelbine and capecitabine
d. None of the above

2. The Canadian trial of mammography shows an improvement in mortality in women under age 50 screened by mammography.
a. True
b. False

3. The updated ATAC trial data continue to demonstrate an efficacy advantage to anastrozole over tamoxifen.
a. True
b. False

4. Intergroup Trial 9741 demonstrated an advantage for which of the following:
a. dose-intense chemotherapy
b. high-dose chemotherapy
c. dose-dense chemotherapy
d. all of the above
e. none of the above

5. The absolute benefit a patient derives from a therapy is independent of that patient's risk of recurrence.
a. True
b. False

6. The IBIS-II trial will evaluate which of the following:
a. anastrozole versus tamoxifen in high-risk women
b. anastrozole versus tamoxifen in women with DCIS
c. anastrozole versus placebo in high-risk women
d. anastrozole versus placebo in women with DCIS
e. b and c

7. Bisphosphonates appear effective in reversing bone loss associated with ovarian ablation and tamoxifen.
a. True
b. False

8. Neutropenia was a significant toxicity in patients receiving dose-dense therapy in CALGB 9741.
a. True
b. False

9. Anastrozole is associated with an increased risk of vaginal bleeding and endometrial cancer.
a. True
b. False

Post-test Answer Key: 1.c, 2.b, 3.a, 4.c, 5.b, 6.e, 7.a, 8.b, 9.b

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Conversations with Oncology Leaders

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Please answer the following questions by circling the appropriate rating:
5 = *Outstanding* 4 = *Good* 3 = *Satisfactory* 2 = *Fair* 1 = *Poor*

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment. 5 4 3 2 1
- Describe and implement an algorithm for HER2-positive breast cancer patients. 5 4 3 2 1
- Develop and explain a management strategy for women with ER-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings. 5 4 3 2 1
- Develop and explain a management strategy for women with ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings. 5 4 3 2 1
- Counsel ER-positive postmenopausal patients about the risks and benefits of aromatase. 5 4 3 2 1
- Evaluate the relevance of emerging data on dose-dense chemotherapy to patients. 5 4 3 2 1

Specific Learning Objectives for Issue 2
Upon completion of this activity, participants should be able to:

- Counsel postmenopausal patients with ER-positive breast cancer regarding updated results of the ATAC trial. 5 4 3 2 1
- Describe the results of Intergroup trial 9741 of dose-dense adjuvant and its implications to patient management. 5 4 3 2 1
- Determine the clinical implications of the recent study showing benefit with the addition of carboplatin to trastuzumab and paclitaxel in patients with HER2-positive metastatic disease. 5 4 3 2 1
- Consider use of the oral fluoropyrimidine prodrug capecitabine alone and in combination with docetaxel in the metastatic setting. 5 4 3 2 1

Overall effectiveness of the activity

Objectives were related to overall purpose/goal(s) of activity 5 4 3 2 1
Related to my practice needs 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

Will the information presented cause you to make any changes in your practice? ___Yes ___No

If Yes, please describe any change(s) you plan to make in your practice as a result of this activity.

_____

What other topics would you like to see addressed in future educational programs?

_____

Degree:

☐ MD ☐ DO ☐ PharmD ☐ RN ☐ NP ☐ PA ☐ BS ☐ Other _____

Breast Cancer™
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