NIH Consensus Development Conference on Adjuvant Therapy for Breast Cancer

November 1–3, 2000
William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

Sponsored by:

♦ National Cancer Institute ♦ Office of Medical Applications of Research ♦

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Contents

III. Adjuvant Hormone Therapy

IV. Adjuvant Chemotherapy

Introduction

The National Institutes of Health (NIH) will sponsor a Consensus Development Conference on Adjuvant Therapy for Breast Cancer on November 1–3, 2000.

Each year, more than 180,000 women in the United States are diagnosed with breast cancer, the most common type of cancer among women in this country. If current breast cancer rates stay constant, a female born today has a 1 in 8 chance of developing breast cancer sometime during her life.

Through continuing research into new treatment methods, women with breast cancer now have more treatment options and hope for survival than ever before. Studies have shown that adjuvant therapy—treatment to kill cancer cells that may have begun to spread, or metastasize, from the breast tumor—given in addition to surgery or other primary therapies increases a woman's chance of long-term survival.

Two types of systemic adjuvant therapy are used for breast cancer, either alone or in combination: adjuvant chemotherapy involves a combination of anticancer drugs; adjuvant hormone therapy deprives cancer cells of the female hormone estrogen, which some breast cancer cells need to grow. In addition to these systemic therapies, radiation therapy is sometimes used as a local adjuvant treatment to help destroy breast cancer cells that have spread to nearby parts of the body.

The rapid pace of discovery in this area continues to broaden the knowledge base from which informed treatment decisions can be made. The purpose of this conference is to clarify, for clinicians, patients, and the general public, various issues regarding the use of adjuvant therapy for breast cancer. After 1½ days of presentations and audience discussion of the latest adjuvant therapy research, an independent, non-Federal consensus development panel will weigh the scientific evidence and draft a statement that will be presented to the conference audience on the third day. The consensus development panel’s statement will address the following key questions:

- **Which factors should be used to select systemic adjuvant therapy?**
- **For which patients should adjuvant hormonal therapy be recommended?**
- **For which patients should adjuvant chemotherapy be recommended? Which agents should be used, and at what dose or schedule?**
- **For which patients should postmastectomy radiotherapy be recommended?**
- **How do side effects and quality-of-life issues factor into individual decision-making about adjuvant therapy?**
- **What are promising new research directions for adjuvant therapy?**

On the final day of the meeting, the panel chairperson, Dr. Patricia Eifel, will read the draft statement to the conference audience and invite comments and questions. A press conference will follow to allow the panel and chairperson to respond to questions from media representatives.

General Information

Conference sessions will be held in the Natcher Conference Center, National Institutes of Health, Bethesda, Maryland. Sessions will run from 8 a.m. to 5:35 p.m. on Wednesday, from 8 a.m. to 1 p.m. on Thursday, and from 9 a.m. to 11 a.m. on Friday. The telephone number for the message center is (301) 496-9966; the fax number is (301) 480-5982.

Cafeteria

The cafeteria in the Natcher Conference Center is located one floor above the auditorium on the main floor of the building. It is open from 7 a.m. to 2 p.m., serving breakfast and lunch.

Sponsors

The primary sponsors of this meeting are the National Cancer Institute (NCI) and the NIH Office of Medical Applications of Research (OMAR). Cosponsors include the National Institute of Nursing Research and the NIH Office of Research on Women's Health.

Statement of Interest

In accordance with ACCME requirements, each speaker presenting at this conference has been asked to submit documentation outlining all outside involvement pertaining to the subject area. Please refer to the chart in your participant packet for details.

Agenda

Wednesday, November 1

7:30 a.m. Registration

8:00 a.m. Opening Remarks
Richard D. Klausner, M.D., Director
National Cancer Institute

8:15 a.m. Charge to the Panel
Barnett S. Kramer, M.D., M.P.H., Director
NIH Office of Medical Applications of Research

8:20 a.m. Panel and Conference Chair Remarks
Patricia Eifel, M.D., Professor of Radiation Oncology
M.D. Anderson Cancer Center

I. Overview

8:30 a.m. Overview of Conference
William C. Wood, M.D., FACS, Joseph Brown Whitehead Professor and Chairman, Department of Surgery
Emory University School of Medicine

II. Factors Used To Select Adjuvant Therapy

8:45 a.m. Factors Used To Select Adjuvant Therapy—Overview
Gary M. Clark, Ph.D., Professor of Medicine
Baylor Breast Center
Baylor College of Medicine

9:05 a.m. Traditional and Newer Pathological Factors
Stuart J. Schnitt, M.D., Associate Professor of Pathology
Harvard Medical School
Director of Surgical Pathology
Beth Israel Deaconess Medical Center

9:25 a.m. Prognostic and Predictive Role of Proliferation Indices
Maria Grazia Daidone, Ph.D.
Unit 10 Determinants of Prognosis and Treatment Response
Department of Experimental Oncology
Istituto Nazionale Tumori

Wednesday, November 1 (continued)

II. Factors Used To Select Adjuvant Therapy (continued)

9:40 a.m. Racial/Ethnic Background and Benefits of Adjuvant Therapy for Breast Cancer
James J. Dignam, Ph.D.
Statistician, National Surgical Adjuvant Breast and Bowel Project

9:55 a.m. Patient-Specific Factors—Young Patients
Aron Goldhirsch, M.D., Chairman, Scientific Committee, International Breast Cancer Study Group
Professor of Medical Oncology and Director, Division of Medical Oncology
European Institute of Oncology

10:10 a.m. Factors Used To Select Adjuvant Therapy: An Overview of Age and Race
Hyman B. Muss, M.D., Associate Director, Vermont Cancer Center
Professor of Medicine, University of Vermont College of Medicine
Director of Hematology/Oncology, Fletcher Allen Health Care
University of Vermont

10:30 a.m. Discussion

III. Adjuvant Hormone Therapy

11:00 a.m. Tamoxifen
Sir Richard Peto, F.R.S., M.Sc.
Early Breast Cancer Trialists' Collaborative Group Secretariat
Professor of Medical Statistics and Epidemiology
Co-Director, ICRF/MRC Clinical Trial Service Unit and Epidemiological Studies Unit
Radcliffe Infirmary, University of Oxford

11:20 a.m. Duration of Adjuvant Hormonal Treatment
Christina Davies, MBChB, M.Sc., ATLAS Coordinator
Clinical Trial Service Unit, Radcliffe Infirmary
University of Oxford

11:35 a.m. Duration of Adjuvant Tamoxifen Therapy
John L. Bryant, Ph.D., Associate Professor of Biostatistics
University of Pittsburgh
Director, Biostatistical Center
National Surgical Adjuvant Breast and Bowel Project

11:50 a.m. Lunch

Wednesday, November 1 (continued)

III. Adjuvant Hormone Therapy (continued)

12:35 p.m. Recent NSABP Adjuvant Studies in Primary (Stage One) Breast Cancer
Bernard Fisher, M.D., Scientific Director
National Surgical Adjuvant Breast and Bowel Project
Distinguished Service Professor
University of Pittsburgh

12:55 p.m. Who Should Not Get Tamoxifen?
C. Kent Osborne, M.D., Professor
Baylor Breast Center
Baylor College of Medicine

1:15 p.m. Hormonal Ablation
Nancy E. Davidson, M.D., Professor
Johns Hopkins Oncology Center
Johns Hopkins University

1:35 p.m. Discussion

IV. Adjuvant Chemotherapy

2:05 p.m. Overview: Progress in Systemic Chemotherapy of Primary Breast Cancer
Gabriel N. Hortobagyi, M.D., FACP, Professor and Chairman
Department of Breast Medical Oncology
M.D. Anderson Cancer Center

2:25 p.m. Is HER-2/neu a Predictor of Anthracycline Utility?—"Pro" Position
Peter Ravdin, M.D., Ph.D., Associate Professor
Department of Medicine, Division of Medical Oncology
University of Texas Health Science Center at San Antonio

2:40 p.m. Is HER-2/neu a Predictor of Anthracycline Utility? No.
George W. Sledge, Jr., M.D., Ballvé-Lantero Professor of Oncology
Department of Medicine
Indiana University School of Medicine

2:55 p.m. Adjuvant Chemotherapy: Taxanes—the "Pro" Position
I. Craig Henderson, M.D., Adjunct Professor of Medicine
University of California, San Francisco

Wednesday, November 1 (continued)

IV. Adjuvant Chemotherapy (continued)

3:10 p.m. NSABP B-28: Initial Results
Eleftherios P. Mamounas, M.D., Medical Director, Cancer Center
Aultman Hospital

3:25 p.m. Taxanes in the Adjuvant Setting: Why Not Yet?
Martine J. Piccart, M.D., Ph.D., Chairman, Breast International Group
Head, Chemotherapy Department
Jules Bordet Institute

3:40 p.m. Discussion

4:15 p.m. Chemoendocrine Combined Therapy
Richard Gray, M.A., M.Sc., Director
Clinical Trials Unit
University of Birmingham Medical School

4:35 p.m. Preoperative Chemotherapy
Norman Wolmark, M.D., Chairman, National Surgical Adjuvant Breast and Bowel Project
Chairman and Professor, Department of Human Oncology
Allegheny General Hospital

4:55 p.m. Who Should Not Receive Chemotherapy?—International Databases
Jonas C. Bergh, M.D., Ph.D., Professor of Clinical and Molecular Oncology
Karolinska Institute and Hospital

5:10 p.m. Who Should Not Receive Chemotherapy?—U.S. Databases and Trials
Monica Morrow, M.D., Professor of Surgery, Northwestern Memorial Hospital, Northwestern University Medical School
Director, Lynn Sage Comprehensive Breast Program
Director, Cancer Department, American College of Surgeons

5:25 p.m.–5:55 p.m. Discussion

5:55 p.m. Adjournment

Thursday, November 2

IV. Adjuvant Chemotherapy (continued)

8:00 a.m. Role of Dose and Dose Intensity for Chemotherapy
Larry Norton, M.D., Head, Division of Solid Tumor Oncology
Norna S. Sarofim Chair in Clinical Oncology
Memorial Sloan-Kettering Cancer Center

8:20 a.m. A Prospective, Randomized Comparison of Two Doses of Combination Alkyating Agents (AA) as Consolidation After CAF in High-Risk Primary Breast Cancer Involving Ten or More Axillary Lymph Nodes (LN): Preliminary Results of CALGB 9082/SWOG 9114/NCIC MA-13
William P. Peters, M.D., Ph.D., Director and Chief Executive Officer
Barbara Ann Karmanos Cancer Institute

8:40 a.m. Overview of the Six Randomized Adjuvant Trials of High-Dose Chemotherapy in Breast Cancer
Karen H. Antman, M.D., Professor of Medicine
College of Physicians and Surgeons of Columbia University
Chief, Division of Medical Oncology
Director, Herbert Irving Comprehensive Cancer Center

9:00 a.m. Discussion

V. Adjuvant Postmastectomy Radiotherapy

9:30 a.m. Overview: Postmastectomy Radiotherapy
Jack Cuzick, Ph.D., Professor of Epidemiology
Head, Department of Mathematics, Statistics, and Epidemiology
Imperial Cancer Research Fund

9:50 a.m. Adjuvant Postmastectomy Radiotherapy: Review of Treatment Guidelines and Techniques
Lori Pierce, M.D., Associate Professor
Department of Radiation Oncology
University of Michigan Medical Center

10:10 a.m. Discussion

Thursday, November 2 (continued)

VI. Influences of Treatment-Related Side Effects and Quality-of-Life Issues on Individual Decision-Making About Adjuvant Therapy

10:45 a.m. Side Effects, Quality-of-Life Issues, and Tradeoffs: Patient Perspective
Amy S. Langer, M.B.A., Executive Director
National Alliance of Breast Cancer Organizations

11:05 a.m. Impact of Tamoxifen Adjuvant Therapy on Symptoms, Functioning, and Quality of Life
Patricia A. Ganz, M.D., Professor
UCLA Schools of Medicine and Public Health
Director, Division of Cancer Prevention and Control Research
Jonsson Comprehensive Cancer Center

11:20 a.m. Chemotherapy and Combined Chemohormonal Therapy
Eric P. Winer, M.D., Associate Professor of Medicine
Department of Adult Oncology, Dana-Farber Cancer Institute

11:40 a.m. Decision-Making Process—Communicating Risks/Benefits: Is There an Ideal Technique?
Mark Norman Levine, M.D., Professor of Medicine
McMaster University

12:00 p.m. Assessing Individual Benefit
Alan Coates, M.D., FRACP, International Breast Cancer Study Group
Chief Executive Officer, Australian Cancer Society

12:20 p.m.–12:50 p.m. Discussion

12:50 p.m. Adjournment

Friday, November 3

8:00 a.m. Registration

9:00 a.m. Presentation of Consensus Development Statement

9:30 a.m. Public Discussion

11:00 a.m. Panel Meets in Executive Session

1:00 p.m. Press Conference

2:00 p.m. Adjournment

Panel Members

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Abstracts

The following are abstracts of presentations to the NIH Consensus Development Conference on Adjuvant Therapy for Breast Cancer. They are designed for the use of panelists and participants in the conference and as a reference document for anyone interested in the conference deliberations. We are grateful to the authors for their participation and for supplying these summaries.

Abstracts for the following presentations do not appear:

Tamoxifen—Sir Richard Peto, F.R.S., M.Sc.

Chemoendocrine Combined Therapy—Richard Gray, M.A., M.Sc.

Role of Dose and Dose Intensity for Chemotherapy—Larry Norton, M.D.

Jeffrey Abrams, M.D.
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Overview of Conference

William C. Wood, M.D., FACS

Carcinoma of the breast remains the most common cancer in women in the United States.

It is exceeded only by lung cancer as a cause of cancer death in women. In the 10 years since the last NIH consensus development conference (CDC) on this subject, large-scale randomized clinical trials have provided further evidence regarding all types of adjuvant therapy. In order to base consensus on clear evidence, the scope of this conference will be limited to operable, invasive breast cancer. This is where the survival of women with breast cancer can be significantly affected by choice of therapy.

The questions to be addressed by the panel meet two criteria:

- They are of crucial interest to breast cancer patients and their health care team.
- A body of scientific evidence exists to allow an informed consensus.

A CDC in 1980 also addressed the efficacy of adjuvant chemotherapy in breast cancer (NIH, 1980). In 1985, another CDC focused on issues of survival and adjuvant chemotherapy and hormonal therapy (NIH, 1986). In 1990, the question of whether breast conservation was appropriate for primary therapy was teamed with consideration of the role of adjuvant therapy in women without lymph node involvement (NIH, 1992). The subsequent decade has seen trials worldwide addressing the combination of chemotherapy with hormonal therapies, the introduction of new cytotoxic agents of great efficacy, questions of dose and schedule, and the evaluation of both prognostic and predictive tumor markers. These were topics recommended for further investigation in the report of the 1990 CDC. There now appears to be sufficient data to discuss the question of when adjuvant therapy is appropriate and the degree to which evidence supports tailoring the therapy to both patient and tumor.

There are new and promising strategies that are still a part of numerous ongoing clinical trials. These include the mapping and evaluation of sentinel lymph nodes to select patients for nodal staging and therapy, and the role of immunohistochemical (IHC) evaluation of bone marrow biopsies. Herceptin as a single agent and in combination with cytotoxic and hormonal agents is emerging as a major subject of large-scale clinical trials addressing schedule, duration, and optimal combination. The role of bisphosphonates as adjuvant therapy and parameters that may predict those patients most likely to benefit from their use are also in the process of definition. The delayed use of chemotherapy or hormonal adjuvant therapy and the role of “maintenance” in adjuvant therapy are being studied in a few trials. At a still earlier phase are trials of small molecule inhibitors, antisense gene constructs, antiangiogenesis compounds, and vaccines. None of these were judged by the planning committee to have sufficient evidence from mature trials to be placed on the agenda at this time, but they are worthy topics for ongoing clinical research.

References

National Institutes of Health. Adjuvant chemotherapy of breast cancer. Consens Dev Conf Summ 1980;3:21-4.

NIH Consensus Development Conference Statement: Adjuvant chemotherapy for breast cancer. September 9-11, 1985. CA Cancer J Clin 1986;36:42-7.

NIH Consensus Development Panel. Treatment of early stage breast cancer. J Natl Cancer Inst Monogr 1992;11:137-42.

Factors Used To Select Adjuvant Therapy—Overview

Gary M. Clark , Ph.D.

The terms “prognostic factors” and “predictive factors” have been used in many different contexts. Some factors may be patient-specific (for example, race, age, socioeconomic, environmental); others may be disease-specific (for example, biomarkers measured on tumor specimens, serum, bone marrow, etc.). These factors have several potential clinical uses, including identifying patients at high risk for a specific disease or for diagnosing that disease, estimating prognosis for patients diagnosed with a specific disease who receive no therapy or standard therapy, predicting response to a particular therapy, monitoring response to therapy during a treatment course, or identifying targets of opportunity for new therapies.

For this presentation, I will focus on prognostic biomarkers that might be used to estimate prognosis for patients diagnosed with a specific disease who receive no therapy or standard therapy, and on predictive biomarkers for predicting response to a particular therapy. Evaluation of prognostic biomarkers requires a single group of patients, preferably untreated. Evaluation of predictive biomarkers requires two groups of patients, preferably randomized to treatment or no treatment. Evidence of predictability is obtained by computing a statistical test for an interaction between treatment and biomarker status.

The clinical endpoints for evaluating prognostic or predictive biomarkers may be overall survival, disease-specific survival, disease-free survival, progression-free survival, event-free survival, tumor response as determined by tumor shrinkage, or modulation of another biomarker. Efficacy may be expressed as absolute benefit or relative benefit. Relative benefit for a survival endpoint is often expressed as the relative risk (risk of dying in the experimental group divided by the risk of dying in the control group), or the relative odds ratio (odds of surviving vs. dying in the experimental group divided by the odds of surviving vs. dying in the control group). The hazard ratio obtained from statistical regression models is often used to approximate the relative risk.

Only recently have criteria been proposed for determining the clinical utility of biomarkers. The American Society of Clinical Oncology (ASCO Expert Panel, 1996) used very conservative criteria to develop practice guidelines for using biomarkers. Partly in response to the lack of consensus about these criteria, a tumor marker utility grading system (TMUGS) was developed to differentiate levels of evidence among published studies (Hayes, Bast, Desch, et al., 1996). The College of American Pathologists used a modification of this system to develop its consensus statements about prognostic factors in breast, colon, and prostate cancer (Fitzgibbons, Page, Weaver, et al., 1999).

Study designs to evaluate biomarkers for different clinical uses vary with respect to the types of subjects and/or tissues to be studied, the endpoints that need to be measured, and the number of subjects and/or tissues that need to be accrued. However, the basic methodological principles for good study designs are common to all clinical uses (Altman, Lyman, 1998). All

study designs should be based on clearly stated hypotheses. Assays should be reproducible and should be performed without knowledge of the clinical data and patient outcome. Results for individual factors should be analyzed using multivariate techniques that incorporate standard biomarkers that are already in clinical use. All results should be validated in subsequent studies before they are incorporated into clinical practice.

Very few new prognostic or predictive factors have been validated and endorsed for clinical use during the past several years. Part of the reason is a lack of adherence to proposed guidelines for the design, conduct, analysis, and reporting of results from prognostic factor studies. It is time to translate the principles of good study design and analysis that have been developed for clinical trials to the evaluation of new biomarkers.

References

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Traditional and Newer Pathological Factors

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During the last two decades there has been an intensive effort by many investigators to identify prognostic and predictive factors for patients with breast cancer. Prognostic factors are defined as those capable of providing information on clinical outcome at the time of diagnosis, whereas predictive factors are defined as those capable of providing information on the likelihood of response to a given therapeutic modality (Gasparini, Pozza, Harris, 1993). Many recent studies have focused on the potential prognostic and/or predictive role of newer biological and molecular markers, such as growth factors and their receptors, oncogenes and tumor suppressor genes and their products, proteolytic enzymes, adhesion molecules, and markers of cellular proliferation and angiogenesis, among others (Mansour, Ravdin, Dressler, 1994). However, studies of such factors have frequently yielded conflicting results and clinical confusion (Loprinzi, Ravdin, de Laurentiis, et al., 1994). Much of the confusion is due to the fact that even studies evaluating the same prognostic marker often differ in patient selection, treatment methods (including the use of systemic therapy), methods for analyzing the marker, methods of statistical analysis, length of patient followup, and prognostic markers to which the "new" marker is being compared.

There is universal agreement that the status of the axillary lymph nodes as determined by routine pathologic evaluation remains the most important prognostic factor for patients with breast cancer (Goldhirsch, Glick, Gelber, et al., 1998). Although there is increasing interest in the use of ancillary techniques, such as immunohistochemistry, to detect occult tumor cells, the clinical significance of occult axillary lymph node metastases detected exclusively by immunohistochemical staining or any other ancillary technique is at present an unresolved issue (Giuliano, Kelemen, 1998).

Among patients with node-negative disease, the important prognostic factors are generally considered to be tumor size, histologic and/or nuclear grade, histologic type, and hormone receptor status (Goldhirsch, Glick, Gelber, et al., 1998). Hormone receptor status is also the most important predictive factor for response to systemic endocrine therapy.

At a recent consensus conference held under the auspices of the College of American Pathologists (Fitzgibbons, Page, Weaver, et al., 2000), a multidisciplinary group of pathologists, clinicians, and statisticians reviewed prognostic and predictive factors in breast cancer and categorized them based on the strength of published evidence into the following groups:

Category I: Factors proven to be of prognostic importance and useful in clinical patient management. Included in this category are tumor size, lymph node status, histologic grade, histologic type, mitotic rate, and hormone receptor status.

Category II: Factors that have been extensively studied biologically and clinically, but whose import remains to be validated in statistically robust studies. This category includes HER-2/neu, p53, lymphovascular invasion, and proliferation markers.

Category III: All other factors not sufficiently studied to demonstrate their prognostic value. Included in this group are DNA ploidy, tumor angiogenesis, epidermal growth factor receptor, transforming growth factor-alpha, bcl-2, pS2, and cathepsin D.

In addition, detailed recommendations for improvement of each factor were made, based on the following goals: (1) to increase the uniformity and completeness of pathologic evaluation; (2) to enhance the quality of data collected about existing prognostic factors; and (3) to improve patient care.

It is of interest to recall that one of the four major issues discussed at the 1990 NIH consensus development conference on the treatment of early breast cancer was the use of prognostic factors to manage patients with node-negative disease. At that conference, a useful prognostic factor was defined as one that had the following characteristics: (1) significant and independent predictive value validated by clinical testing; (2) identification that was feasible, reproducible, and widely available with quality control; and (3) ease of interpretation by clinicians and having therapeutic implications (NIH Consensus Conference, 1991). Even at this time, 10 years later, few, if any, of the numerous reported prognostic or predictive factors fulfill all three of these criteria.

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Prognostic and Predictive Role of Proliferation Indices

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Proliferative cellular activity is one of the biological processes most thoroughly investigated in breast cancer for its association with neoplastic progression and metastatic potential. Several approaches, in addition to the mitotic activity component of all pathologic grading systems, have been used by pathologists and cell biologists to determine and quantify the whole proliferative fraction or discrete fractions of cells in specific cell cycle phases on consecutive series of clinical tumors. Such approaches are based on different rationales, including detection of proliferation-related antigens by way of the Ki-67/MIB-1 labeling index and evaluation of the S-phase cell fraction by quantifying nuclear DNA content or cells incorporating DNA precursors (labeled pyrimidine bases, such as ^{3}H-thymidine, or halogenated analogs, such as bromo- or iododeoxyuridine). These approaches employ different methods of evaluation (immunocytochemistry, cytometry, or autoradiography), and each has advantages and disadvantages, including different feasibility rates. Moreover, the different measures of proliferation do not always prove to correlate with each other in terms of biological or clinical significance when comparatively analyzed on the same case series and may present slightly varying sensitivity and specificity rates.

In general, cell proliferation has proved to be associated with breast cancer prognosis, even though its prognostic power tends to decline over time, at least for the flow-cytometric S-phase cell fraction (FCM-S) (Bryant, Fisher, Gunduz, et al., 1998). In patients with node-negative breast cancer treated with local-regional therapy alone until relapse, and in the presence of traditional prognostic factors (age, tumor size, estrogen receptor [ER], and progesterone receptor [PgR]), the S-phase fraction (evaluated as ^{3}H-thymidine labeling index [TLI], considered as a continuous variable and categorized by tree-structured regression analysis) can be used to identify subsets at different 8-year risk of local-regional relapse (in association with patient age) or distant metastasis (in association with tumor size and patient age). Cell proliferation is the only prognostic discriminant for intermediate-size (1-2 cm) tumors, whereas it is not predictive for contralateral cancer (Silvestrini, Daidone, Luisi, et al., 1995). In general, the prognostic information provided by FCM-S, TLI, or the Ki-67/MIB-1 index is confirmed in multivariate analyses, including DNA ploidy, p53 and bcl-2 expression, ER and PgR status, and histologic or nuclear grade (Wenger, Clark, 1998; Scholzen, Gerdes, 2000). This information helps to identify tumor phenotypes associated with a high risk of relapse (high cell proliferation, alone and in association with other unfavorable factors, such as young age, tumor size >2 cm, high pathologic grade, absence of ER or PgR, alterations in oncogenes or in tumor suppressor genes) and with low risk of relapse (low cell proliferation associated with older age, tumor size ≤2 cm, low pathologic grade, presence of ER or PgR, absence of genomic alterations).

All of these results, however, have been derived from investigations not specifically planned to determine the clinical utility of the biomarker and, in terms of quality of information, the outcomes of the studies can be considered to be only hypothesis-generating, with the advantage of long-term followup counterbalanced by marked heterogeneity in technical and

analytical procedures. The usefulness of prognostic indicators in patient management can be tested in the context of randomized treatment protocols in which evaluation of the utility of biological information accounts for the primary or secondary objective with an improved level of evidence (LOE) of results, as in the following:

- **Confirmatory studies to validate proliferative activity for identifying subsets of patients at very low risk of relapse.** Evidence in favor of such a hypothesis is supported by the preliminary outcome of a large LOE I study on node-negative breast cancers (Hutchins, Green, Ravdin, et al., 1998) in which patients presenting with ER- or PgR-positive, intermediate size tumors with a low FCM-S exhibited an excellent prognosis without adjuvant treatment (5-year disease-free survival [DFS], 88 percent), similar to patients with tumors ≤1 cm in diameter. The result has been independently confirmed on a substantial series of node-negative tumors in a prospective investigation (Jones, et al., 1999), in which Ki-67/MIB-1 was considered in addition to FCM-S. It has also been confirmed in a study derived from cases enrolled in a large randomized clinical trial (NSABP B-14) that evaluated the effectiveness of adjuvant tamoxifen in patients with ER-positive cancers (Bryant, Fisher, Gunduz, et al., 1998). The latter study demonstrated the heterogeneous clinical outcome of patients with tumors traditionally considered at low risk and showed that FCM-S (as a continuous variable), patient age, tumor size, and PgR better differentiated the risk subsets, with the 10-year DFS rate ranging from 85 percent to 30 percent and overall survival rate from 95 percent to 40 percent. On the basis of such a clinical and pathobiological classification, it seems unlikely that the addition of adjuvant chemotherapy to tamoxifen will improve clinical outcome in women at very low risk of relapse.

  For high-risk (ER-negative, node-negative) tumors, however, the long-term results of a prospective randomized trial evaluating the effectiveness of adjuvant CMF confirmed the efficacy of treatment (Zambetti, Valagussa, Bonadonna, 1996). There was a benefit against both slowly and rapidly proliferating tumors that was more evident for the latter.

- **Clinical utility of proliferative activity for treatment decisionmaking in high-risk node-negative breast cancer patients.** To test the improvement in clinical outcome following adjuvant chemotherapy in high-risk cases defined on the basis of tumor proliferative activity, a prospective multicentric trial was conducted between 1989 and 1993 (Amadori, Nanni, Marangolo, et al., 2000). In that trial, patients with high-TLI tumors were randomized to receive either CMF or no further treatment following surgery ± radiotherapy. At a median followup of 80 months, relapses had occurred in 28 of the 137 patients who received CMF and in 47 of the 141 patients treated with local-regional therapy alone. A reduction in the annual relapse risk of about 40 percent with chemotherapy treatment was associated with an 11 percent absolute benefit for 5-year DFS (83 percent [95 percent CI, 77-89] for CMF-treated patients versus 72 percent [95 percent CI, 65-79] for untreated patients, p=0.028). Also shown was a reduction of both local-regional (from 6.4 percent to 2.9 percent) and distant relapses (from 21.3 percent to 12.4 percent). The benefit of CMF treatment was most evident in

cases at high risk—that is, with TLI values in the second (DFS: 88 percent versus 78 percent, p=0.037) and third tertile (DFS: 78 percent versus 58 percent, p=0.024).

In summary, the results support the use of cell proliferation to select high-risk patients with node-negative tumors. The finding of a higher benefit from antimetabolite-based regimens in tumors with the highest proliferation is in keeping with the evidence from retrospective studies (to be prospectively validated) that proliferation indices may be used to help predict treatment response in adjuvant and neoadjuvant settings (Wenger, Clark, 1998).

In addition, cell proliferation can provide information regarding the efficacy of different treatment schedules. In an ancillary study analyzing 70 percent of the cases entered in a randomized treatment protocol designed to compare alternating versus sequential regimens of doxorubicin and CMF in breast cancer patients with more than three positive axillary lymph nodes, the benefit of sequential administration was mainly evident in patients with tumors with low to intermediate proliferation rates (Silvestrini, Luisi, Zambetti, et al., 2000).

Methodologically, proliferation indices in part fulfill common requirements for clinical use in terms of technical-biological effectiveness. They have been proven to describe the specific biological phenomenon, as well as to provide results that are informative and rapidly obtainable at a reasonable cost when needed for clinical decisionmaking.

However, further effort should be devoted to standardizing methodologies and interpretation criteria (mainly for FCM-S results) to improve the reliability, accuracy, and reproducibility of assay results within and among different laboratories by promoting and maintaining quality control programs (found in several countries for FCM-S and TLI), and to establishing guidelines for classifying tumors according to proliferative activity. There should also be guidelines for reporting and comparing results. All of these factors, in addition to the inherent heterogeneity of case series, could account for the variability seen in results.

In terms of clinical effectiveness, proliferation indices need to be further validated in the context of randomized trials to assess their utility to identify low-risk patients (both in the presence of traditional prognostic factors, including pathological grade, and in cases diagnosed in recent years that are possibly epidemiologically and biologically different from those diagnosed in prior decades) and to make decisions about whether to use specific adjuvant therapies.

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Racial/Ethnic Background and Benefits of Adjuvant Therapy for Breast Cancer

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Variation in breast cancer survival by racial/ethnic background has been noted in many studies, as well as in summaries of national cancer statistics (Greenlee, Murray, Bolden, et al., 2000). Numerous factors have been implicated as sources of these differences, including clinical and pathologic features of the disease indicative of poor prognosis, economic resource inequities and other social factors, and disparities in treatment access and (possibly) efficacy. After a brief review of these factors, we examine the available data from randomized clinical trials, where disease stage is comparable and treatments are uniformly delivered. We also consider studies conducted in settings where uniformity of disease diagnosis and care can be reasonably assumed. Using this information, we address (1) whether outcomes among women of different racial origins are more similar within these settings than outcomes observed in the population at large, and (2) whether there is evidence of differential efficacy of adjuvant therapy according to race.

Disparity in breast cancer prognosis between African Americans and Caucasians has been attributed to clinical and demographic characteristics, pathologic and biologic disease features, and socioeconomic status and related health care factors (Dignam, 2000). African American women are more often diagnosed at a later stage of the cancer, tend to be younger at diagnosis, and more often exhibit less favorable tumor characteristics. Several studies also have found disparities in health care, including less frequent administration of care in accordance with established guidelines. Limited studies of Asian Americans, who tend to have a lower incidence of breast cancer, indicate equal or better prognosis than that of whites, in part due to earlier stage at diagnosis and favorable disease features (Boyer-Chammard, Taylor, Anton-Culver, 1999). Studies of Hispanic women have generally found the prevalence of poor prognosis indicators to be intermediate between those of blacks and whites (Elledge, Clark, Chamness, et al., 1994). In general, survival comparisons among women whose cancer is at a comparable stage from any racial background are considerably more similar than those seen when overall rates are compared, but some residual disparities remain.

Among the major studies addressing disparities between blacks and whites, it has been found, in most cases, that a primary explanatory factor, such as disease stage at diagnosis, does not fully account for the difference between the groups, but when additional factors are taken into account the outcomes are similar. Results derived among patients participating in randomized clinical trials are particularly illustrative of this point. The Cancer and Leukemia Group B (CALGB) study compared characteristics and outcomes for blacks and whites participating in a trial of adjuvant chemotherapy for node-positive breast cancer (Roach, Cirrincione, Budman, et al., 1997). The authors found blacks to be younger at diagnosis and to have larger tumors that were more often estrogen receptor (ER)-negative. Excess risk of death among blacks relative to whites (and others) was reduced from 35 percent to 14 percent after taking into account these prognostic factor differences. Excess risk of recurrence or death for blacks was reduced from 24 percent to 7 percent. Recently, analyses of outcomes among African

Americans and Caucasians participating in studies of the Eastern Cooperative Oncology Group (ECOG) were presented (Yeap, Zelen, 2000). In that study, black women participating in ECOG adjuvant breast cancer trials between 1983 and 1995, matched with white women of similar age, treating institution, and treatment arm, had comparable survival outcomes. Estimates of treatment effects within race groups were not presented in these studies, and such analyses are generally not warranted unless there is statistical evidence of differential treatment efficacy (e.g., interactions) between race and treatment group. Furthermore, such analyses are hindered by low statistical power.

Previously published results from two National Surgical Adjuvant Breast and Bowel Project (NSABP) trials similarly indicated that when stage of disease and treatment are comparable, outcomes for African Americans and Caucasians do not differ markedly (Dignam, Redmond, Fisher, et al., 1997). In that study we focused on patients with node-negative breast cancer and examined outcomes separately by ER status, which has been implicated as an important explanatory factor in disparities between these groups. Results indicated equal disease recurrence risk and statistically nonsignificant 10 percent excess in mortality for blacks after adjustment for prognostic factors. Among women with ER-negative tumors receiving chemotherapy, a reduction in disease-free survival (DFS) events of 32 percent was noted among blacks, compared to 36 percent for whites. Among patients with ER-positive tumors receiving tamoxifen, reductions in DFS events were 20 percent for blacks and 39 percent for whites. Statistical evidence of a differential treatment response by race was not noted. This latter finding is further supported by a recent study finding a comparable reduction in contralateral breast cancer incidence among African American and Caucasian patients receiving tamoxifen in NSABP breast cancer treatment trials (McCaskill-Stevens, Bryant, Costantino, et al., 2000). Newly examined data from NSABP trials among node-positive patients have also shown comparable prognosis and extent of treatment benefit among black and white participants.

Observational retrospective studies evaluating outcomes in health care systems where treatment is uniform have been presented as evidence of the efficacy of established treatment regimens among minority patient populations (Briele, Walker, Wild, et al., 1990; Heimann, Ferguson, Powers, et al., 1997; Yood, Johnson, Blount, et al., 1999). As in clinical trials, results of these studies suggest that, for patients treated in accordance with recommendations for their clinical and pathologic disease presentation, outcomes and extent of benefit among African Americans and Caucasians are comparable. Studies of treatment patterns in these settings can also serve to evaluate the extent to which current treatment guidelines are observed in certain patient populations (Muss, Hunter, Wesley, et al., 1992; Breen, Wesley, Merrill, et al., 1999).

In summary, women of different race backgrounds, diagnosed at comparable disease stage and appropriately treated, tend to experience similar breast cancer prognosis. From the clinical trial data and studies from equal-care settings, it may be indirectly inferred that treatment benefits are comparable across race groups. However, important clinical and pathologic disease characteristics may place certain women at increased risk of poor outcome, and warrant continued study as to how and why these may be related to race. Although demographic classification in National Cancer Institute-sponsored clinical trials has been found to be generally representative of the incident cancer burden in the population (Tejeda, Green, Trimble, et al., 1996), increased racial/ethnic diversity in clinical trial participation would be beneficial. More diverse participation will ensure dissemination of quality care in accordance with current

treatment guidelines and will provide the necessary data for future investigations of the role of race in breast cancer treatment.

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Patient-Specific Factors—Young Patients

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Breast cancer rarely occurs in young women. About 2 percent of female patients with the disease are less than 35 years old at diagnosis (NCI, 2000). Below the age of 20 the incidence is estimated to be 0.1 per 100,000 women, increasing to 1.4 for those 20 to 24 years old, 8.1 for those 25 to 29 years old, and 24.8 for those 30 to 34 years old (NCI, 2000). Breast cancer at a young age has a more aggressive biological behavior and is associated with a more unfavorable prognosis than when the disease arises in older patients. Specifically, tumors in younger women are less well differentiated (higher grade) and have a higher proliferating fraction and more vascular invasion than those occurring in older patients (Walker, Lees, Webb, et al., 1996; Adami, Malker, Holmberg, et al., 1986; Chung, Chang, Bland, et al., 1996; Kollias, Elston, Ellis, et al., 1997). A larger number of positive axillary lymph nodes are detected in young than in older patients. Results from two population-based studies indicate that the risk of death is highest among the youngest and the oldest cohorts when compared with patients of intermediate age (Adami, Malker, Holmberg, et al., 1986), even when the analysis allows for differences in initial tumor stage (Kollias, Elston, Ellis, et al., 1997).

A review of the National Cancer Data Base reveals that patients younger than 35 years of age have more advanced disease at diagnosis and a poorer 5-year survival rate than older premenopausal patients (Winchester, Osteen, Menck, et al., 1996). Similar findings have been reported from the National Cancer Institute SEER database (Swanson, Lin, 1994), from the Finnish Cancer Registry (Holli, Isola, 1997), and from a recent Danish study on young patients who did not receive adjuvant therapy (Kroman, Jensen, Wohlfahrt, et al., 2000), as well as from several series described from single centers (Albain, Allred, Clark, 1994; Noyes, Spanos, Montague, 1982; Ribeiro, Swindell, 1981).

Typically, young patients receive chemotherapy, and in many countries clinicians have been reluctant to employ ovarian ablation or other endocrine treatment (Kroman, Jensen, Wohlfahrt, et al., 2000). No adjuvant systemic therapy was prescribed to young women with early stage breast cancer thought to have favorable prognostic factors in a large Danish study (Kroman, Jensen, Wohlfahrt, et al., 2000). In that study, which included 10,356 women with primary breast cancer who were less than 50 years old, the youngest (predefined as having a low-risk disease and therefore given no adjuvant systemic treatment) had a significantly increased risk of dying. The increased risk with decreasing age at diagnosis (adjusted relative risk [RR] with a cohort 45 to 49 years of age as a reference group having a RR of 1) was 1.12 (95 percent confidence interval [CI] 0.89 to 1.40) for 40 to 44 years of age, 1.40 (1.10 to 1.78) for 35 to 39 years of age, and 2.18 (1.64 to 2.89) for <35 years of age. No such trend was seen in patients who were considered at the time of the study to be eligible to receive adjuvant cytotoxic

treatment. Thus, the negative prognostic effect of young age was confined to those who did not receive adjuvant cytotoxic treatment, leading to the conclusion that young women with breast cancer, on the basis of age alone, should be regarded as high-risk patients and be given adjuvant cytotoxic treatment. This conclusion relies on the assumption that a worse prognosis predicts responsiveness to chemotherapy.

The International Breast Cancer Study Group (IBCSG) treated 3,700 pre- and perimenopausal patients with various timing and duration of adjuvant cyclophosphamide, methotrexate, and fluorouracil (classical CMF with or without low-dose prednisone, with or without oophorectomy) (Aebi, Gelber, Castiglione-Gertsch, et al., 2000). Of these women, 314 were less than 35 years of age at study entry. The trials were conducted between 1978 and 1993. Relapse and death occurred earlier and more often in younger (<35 years) than in older (≥35) patients. The 10-year disease-free survival rate (DFS; ± SE) was 35 percent (±3) vs. 47 percent (±1) (hazards ratio [HR], 1.41; 95 percent CI, 1.22 to 1.62; $p<0.001$) and overall survival was 49 percent (±3) vs. 62 percent (±1) (HR, 1.50; 95 percent CI, 1.28 to 1.77; $p<0.001$), respectively. Younger patients with estrogen receptor positive (ER+) tumors had a significantly worse prognosis than younger patients with estrogen receptor negative (ER–) tumors. The 10-year DFS was 25 percent (±4) vs. 47 percent (±5); HR, 1.49; 95 percent CI, 1.09 to 2.04; $p=0.014$.

In contrast, among older patients the prognosis was similar for patients with ER+ compared with patients with ER– tumors (10-year DFS 45 percent [±1] vs. 46 percent [±2]; HR, 0.94; 95 percent CI, 0.85 to 1.04; $p=0.27$). The largest difference in 10-year DFS between younger and older patients was observed for those with ER+ tumors who did not achieve amenorrhea (23 percent [±6] vs. 38 percent [±3]; HR, 1.67; 95 percent CI, 1.19 to 2.34; $p=0.003$). This retrospective analysis of treatment outcome suggests that the endocrine effects of chemotherapy alone were insufficient for the younger age group (only about 30 percent of the patients had some cessation of menses from the 12–6 courses of classical CMF). Additional endocrine therapies (tamoxifen or ovarian ablation, or a combination of both) should be considered for these patients if their tumors express steroid hormone receptors. Such endocrine therapies might be the most effective component of their adjuvant treatment program.

Additional issues to be considered when approaching treatment and personal decisions for young patients with breast cancer (excluding issues related to genetic predisposition) are included in table 1.

Treatment decision-making for very young women with newly diagnosed breast cancer may be affected by the strong emotional involvement of care providers. Furthermore, the belief that an increased risk of relapse justifies use of cytotoxics to increase the demise of cancer cells might also contribute to lack of progress in evaluating endocrine therapies for this rare presentation of breast cancer.

Table 1. Treatment and personal issues: evidence and current options

Issue for Discussion	Status of Evidence	Current Options (Sometimes Despite Evidence)
Local disease control, very late effects of radiation therapy	Young patients have a higher risk for locoregional relapse (Kim, Simkovich-Heerdt, Tran, et al., 1998; Elkhuizen, van de Vijver, Hermans, et al., 1998). No data on late effects on the heart of anthracyclines and taxanes plus radiation therapy.	Breast conservation with radiation therapy is considered a standard treatment (Guenther, Kirgan, Giuliano, 1996). Total or bilateral (prophylactic) mastectomy is increasingly discussed (Schrag, Kuntz, Garber, et al., 1997).
Pregnancy after breast cancer	Pregnancy seems to be safe after breast cancer and after adjuvant systemic cytotoxic therapy (Kroman, Jensen, Melbye, et al., 1997; Velentgas, Daling, Malone, et al., 1999; Gelber, Coates, Goldhirsch, et al., in press), (except for BRCA1 and BRCA2 carriers) (Jernstrom, Lerman, Ghadirian, et al., 1999). Uncertainty about pretreatment with tamoxifen and neonatal genital tract malformations (Nakai, Uchida, Teuscher, 1999).	Reluctance to consider pregnancy even for women with node-negative disease (Surbone, Petrek, 1997). Availability of GnRH analog as an effective endocrine treatment, especially if given with tamoxifen (Boccardo, Rubagotti, Amoroso, et al., 2000). New endocrine therapies are being investigated, mainly in postmenopausal patients.
Interpersonal and family relations	Younger women might be particularly vulnerable to the emotional distress of the disease (Northouse, 1994).	Psychological support (trials are testing this type of intervention).

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Factors Used To Select Adjuvant Therapy: An Overview of Age and Race

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Age, race, and socioeconomic status all play a role in decisions about adjuvant therapy for breast cancer. Age is important for two major reasons: first, because it remains the major risk factor for breast cancer; and second, because the potential benefits of adjuvant therapy diminish as competing causes of mortality (comorbidity) increase. More than half of all new breast cancers in the United States occur in women 65 and older, a statistic that has strong meaning in a population whose longevity is increasing (Yancik, 1997). In addition, comorbidity significantly increases with increasing age, and comorbidity has a major effect on patient survival (Fleming, Rastogi, Dmitrienko, et al., 1999). Race is especially important because breast cancer mortality is higher in African Americans than in white Americans. Such differences are related to several factors, including stage at presentation, tumor biology, and sociodemographic characteristics (Eley, Hill, Chen, et al., 1994).

Compelling data from a worldwide meta-analysis of adjuvant therapy showed that for older patients with estrogen receptor (ER) or progesterone receptor (PR) positive tumors, tamoxifen significantly increased both the amount of time free from relapse and time of overall survival (EBCTCG, 1998a). Women 70 years and older who took 5 years of tamoxifen had a 54 percent decrease in the annual odds of breast cancer recurrence and a 34 percent decrease in the annual odds of dying of breast cancer. Chemotherapy alone has not been adequately studied in older patients, and in the same overview less than 700 women 70 years and older were entered on randomized trials. Chemotherapy is associated with significant improvements in both relapse-free and overall survival in women ages 50 to 69 years (20.3 percent and 11.3 percent reduction in annual odds of relapse and death, respectively) (EBCTCG, 1998b), but further trials are needed that factor in the effects of comorbidity on treatment outcome, treatment-related toxicity, and quality of life for older women. The potential benefits of adjuvant therapy in older women have recently been estimated using a mathematical model (Extermann, Balducci, Lyman, 2000); it is clear that the value of adjuvant therapy diminishes substantially as age and comorbidity increase, and as non-breast-cancer-related illness becomes a major competing cause of death. What also seems clear is that older women in good general health tolerate standard chemotherapy regimens almost as well as younger women (Christman, Muss, Case, et al., 1992). In the absence of a trial, the recommendations for adjuvant therapy made by an international consensus panel appear prudent and should be used as a treatment guideline (Goldhirsch, Glick, Gelber, et al., 1998). Future clinical research in this setting should focus on adjuvant trials directed at older patients. In addition to relapse-free and overall survival, these trials should have quality of life, functional status, and comorbidity assessment as key endpoints.

African Americans and other minorities are frequently underrepresented in adjuvant trials but available data suggest that, at least for African Americans, the benefits of therapy are similar to those for white women when outcomes are adjusted for stage, comorbid illness, and pathologic and sociodemographic variables (Dignam, 2000). Of note, many trials have shown

small but potentially important biological differences in breast cancer between African American and white patients. African American patients are more likely than whites to have more biologically aggressive, hormone receptor (HR) negative tumors that may limit the potential life-prolonging benefits of tamoxifen therapy (or ovarian ablation) (Elledge, Clark, Chamness, et al., 1994). In large numbers of patients these small differences in tumor biology may prove to be highly meaningful. Little data are available on Hispanic patients and other minorities concerning the risks and benefits of adjuvant therapy. Available data suggests that Hispanic patients with early breast cancer have a prognosis that lies between those for African American and white patients (Elledge, Clark, Chamness, et al., 1994). The data also suggest that for Hispanics, as for African Americans, socioeconomic factors play a key role in the outcome (Franzini, Williams, Franklin, et al., 1997). A key concern for African American patients and other minorities is access to high quality care, including clinical trials. Major efforts by the NCI and other organizations to improve access of minorities to clinical trials are underway. Poverty is associated with poorer cancer outcomes for all Americans irrespective of racial or ethnic group, and remains a national issue (McWhorter, Schatzkin, Horm, et al., 1989).

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Duration of Adjuvant Hormonal Treatment

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Summary. Large trials of 10 years versus 5 years of adjuvant tamoxifen therapy are still in progress. Other large trials have shown that 7 to 8 years of adjuvant tamoxifen treatment are significantly better than 2 to 3 years, with much of the additional benefit emerging after year 5. Large trials have also shown that 5 years of tamoxifen is significantly better than 2 to 3 years. Whatever the hormonal treatment to be used, large-scale randomized evidence is needed as to whether the duration of hormonal therapy should in general be at least 10 years, or whether 7.5 years, or even 5 years, can suffice.

Five years of tamoxifen versus a shorter period. In trials of tamoxifen versus no tamoxifen and of one tamoxifen duration versus another duration (shorter versus longer), the overview has demonstrated that for women with potentially hormone-sensitive disease, tamoxifen is of substantial benefit (EBCTCG, unpublished data, 2000). Five years of tamoxifen appears to be better than shorter regimens at least in terms of recurrence, although this has not been shown so far to be translated into a survival benefit. A French trial of 7 to 8 years of tamoxifen versus 2 to 3 years also shows that, with regard to recurrence, longer is better (Delozier, Spielmann, Mace-Lesec'h, et al., 1997). However, there is inadequate randomized evidence about the effects of prolonging tamoxifen beyond 7 to 8 years. Five years of tamoxifen increases endometrial cancer mortality, and this adverse effect increases with a longer duration of tamoxifen (EBCTCG, 2000; EBCTCG, 1998). In addition, tamoxifen causes a slight increase in the risk of pulmonary embolus (EBCTCG, 2000; EBCTCG, 1998). But tamoxifen reduces the risk of new cancers in the opposite breast, and this effect is also increased with longer duration (EBCTCG, 2000; EBCTCG, 1998). There was no evidence of an effect on mortality from causes other than breast or endometrial cancer. In terms of the 10-year incidence of new cancers, the extra number of endometrial cancers caused by tamoxifen is smaller than the number of new cancers prevented in the opposite breast; the overall net survival benefit is 30 times greater than the hazard.

Five years of tamoxifen versus a longer period. The question of the value of 5 years of tamoxifen versus a longer period is still unanswered in terms of recurrence and survival. So far, that question has not been properly studied, either through indirect comparisons of duration between trials of tamoxifen versus no tamoxifen, or through direct comparisons in trials which compare, within the same study, 5 years of tamoxifen versus longer treatment (EBCTCG, 2000; Peto, 1996; Swain, 1996). Concerns have been expressed about resistance to tamoxifen with more prolonged treatment, but the mechanisms of resistance are poorly understood and, more importantly, this concern has not been supported by randomized evidence. The current trials are of insufficient size—even in combination—to detect the moderately sized difference that might exist. The three directly randomized comparisons of 5 years versus 10 years of adjuvant tamoxifen that started long enough ago to have produced some results have now ended (Tormey, Gray, Falkson, 1996; Stewart, Forrest, Everington, et al., 1996; Fisher, Dignam, Bryant, et al., 1996). All three (known colloquially as ECOG, Scottish Cancer Trial, and NSABP B-14) involved

only small numbers of breast cancer recurrence or death after year 5. It remains quite possible, based on current evidence, to hope for additional benefit from longer treatment, and the results from the French trial support this (Delozier, Spielmann, Mace-Lesec'h, et al., 1997).

The need for large-scale randomized evidence. Studies assessing the optimal duration of adjuvant tamoxifen need to be much larger than has generally been recognized. Small-scale studies carry the substantial risk of getting the wrong answer because their results are unduly influenced by favorable or unfavorable random fluctuations. That is particularly the case if frequent interim analyses are carried out before sufficient numbers of events have been allowed to occur. As a consequence, chance "blips," suggesting either benefit or hazard, are then inappropriately emphasized.

The need for long-term followup. Tamoxifen has a substantial carry-over benefit, with fewer recurrences seen for a few years after the end of the treatment period. This means that, in trials of tamoxifen versus no tamoxifen, the benefits of tamoxifen are enhanced compared with the no tamoxifen arm, but in trials of longer versus shorter tamoxifen there may be little additional benefit apparent during the first few years of continued treatment due to the carry-over benefit in women in the shorter tamoxifen arm of the trial. Any worthwhile benefit will emerge later on, provided that the study is large enough. This means that in trials of longer versus shorter treatment, long-term followup is required, because the expected balance of risks and benefits may change during the followup period. If the question of 5 years versus 10 years is going to be reliably answered, tens of thousands of women may need to be randomized and followed up for at least 10 years. It will probably not be until 2005, or more likely 2010, that there will be sufficient randomized evidence on 5 versus 10 years of tamoxifen to merit a review by the EBCTCG.

Current large-scale trials of 5 versus 10 years of tamoxifen. ATLAS and aTTom are both large-scale randomized trials of longer versus shorter hormonal therapy to assess reliably the effects of an extra 5 years of tamoxifen in women who have had some years of treatment and for whom there is uncertainty as to whether they should stop or continue (Rea, Poole, Gray, 1998). About 20,000 women will be randomized, usually after about 5 years of tamoxifen, to either stop tamoxifen or to continue it for 5 more years. The main analyses in ATLAS and aTTom will be of all-cause mortality, but they will also provide information on cause-specific mortality and on nonfatal but important events. If, by 2010, patients show improved long-term survival with 10 years of tamoxifen, this result will save thousands of lives annually, and will be relevant to the use of hormonal therapies in general. By November 2000, more than 7,000 women will have entered ATLAS, making it the largest-ever study of tamoxifen duration. Some 4,000 have been randomized in aTTom. Still, many thousands more need to be studied in randomized trials to obtain reliable answers about treatment of an extra 5 years with tamoxifen.

Conclusion. There is now reliable evidence that 7 to 8 years of tamoxifen is better than shorter regimens in women with hormone-sensitive breast cancer. There is insufficient evidence to draw reliable conclusions about whether 10 years of tamoxifen compared with 5 years confers additional benefits. ATLAS and aTTom, in combination with the trials of 5 years versus longer adjuvant tamoxifen that have now ended, should help to answer this question, but it is unlikely that a reliable answer will emerge before 2010.

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Duration of Adjuvant Tamoxifen Therapy

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Clinical trials of adjuvant tamoxifen have convincingly demonstrated benefits for patients with estrogen receptor (ER)-positive breast cancer, regardless of nodal status, age, or menopausal status (EBCTCG, 1998; Fisher, Dignam, Bryant, et al., 1996). But despite the large number of trials, there is still uncertainty regarding the optimal duration of tamoxifen therapy. This review will address comparisons of duration of tamoxifen treatment up to about 5 years (about which considerable evidence has been reported in the past decade), and conclude with a summary of trials which have compared 5 years of treatment with longer durations (for which the evidence is not extensive).

Durations Up To 5 Years

Four trials which have been reported in the past decade present direct comparisons of the worth of about 5 years of tamoxifen to shorter durations. Two Eastern Cooperative Oncology Group (ECOG) trials (E4181 and E5181) compared 1 to 5 years of tamoxifen in post- and premenopausal node-positive patients, respectively (Falkson, Gray, Wolberg, et al., 1990; Tormey, Gray, Abeloff, et al., 1992). The Swedish Breast Cancer Cooperative Group (SBCCG) and Cancer Research Campaign (CRC) trials were larger studies comparing 2 to 5 years of treatment (SBCCG, 1996; CRC, 1996). A fifth trial (TAM-01), which was reported in abstract form in 1997, is designed to compare 2 to 3 years duration to 12 to 13 years, but the mean followup available as of the report was 4.5 years, so that currently available data from this trial might best be interpreted as comparing 2 to 3 years with 6 to 7 years (Delozier, Spielmann, Mace-Lesec'h, et al., 1997). All five studies have reported statistically significant reductions in event rates in favor of the longer duration. The three studies comparing about 2 to at least 5 years (SBCCG, CRC, TAM-01) all estimated a reduction in the event rate of about 20 percent. Only one (SBCCG) demonstrated a statistically significant survival advantage for the longer duration (18 percent reduction in mortality rate, SD 7 percent), with one other trial (CRC) also showing a modest but nonsignificant survival advantage (11 percent reduction, SD 13 percent). In light of the evidence for a reduced recurrence rate, it may be reasonable to attribute this to the relatively short followup reported to date, and to the well-known carryover effect of treatment with tamoxifen (EBCTCG, 1998; Fisher, Dignam, Bryant, et al., 1996). Indirect comparison trials of about 1, 2 or 5 years duration based on the 1998 EBCTCG overview lead to a similar conclusion, since the trends of a reduced recurrence rate and reduced mortality over this time range were strongly significant.

Five Years Treatment Versus Longer Duration

Three trials comparing 5 years of tamoxifen to longer periods of time were first reported in 1996. These included NSABP B-14, a double-blind comparison of 5 additional years of

tamoxifen versus placebo in 1,172 node-negative women who had completed 5 years of initial treatment disease-free; the Scottish trial, in which 342 predominately node-negative women were assigned to indefinite tamoxifen or observation following the completion of 5 years of tamoxifen disease-free; and ECOG E4181/E5181, in which 87 postmenopausal node-positive women from E4181 and 107 premenopausal node-positive women from E5181 who were disease-free at 5 years were randomized to either indefinite tamoxifen or observation. All patients in B-14 were ER-positive (≥10 fmol/mg protein), compared to 73 percent in the ECOG trial. In the Scottish trial, 39 percent of the patients had tumors with ≥20 fmol/mg, 22 percent had ≤19 fmol/mg, and 39 percent were not assayed. The NSABP data have recently been updated; the Scottish and ECOG data will be updated at the EBCTCG meeting in 2000.

After a median followup from re-randomization of 6.75 years, the B-14 data indicate no advantage for continued tamoxifen, and in fact trend in the opposite direction. Disease-free survival (DFS) 7 years following re-randomization was 82 percent for placebo patients and 78 percent for those receiving more than 5 years of tamoxifen (HR=1.3, p=0.03). Overall survival was 94 percent for placebo patients and 91 percent for tamoxifen patients (39 versus 57 deaths, HR=1.5, p=0.07). The distribution of first events is shown in table 1. Events in the primary NSABP DFS analysis included recurrence, contralateral breast cancer (CBC), second primary cancer, and death. Table 1 shows that only about one-half (118 of 243) of all first events were "breast cancer related" (i.e., recurrences or CBC). To facilitate comparison with results of the ECOG trial described below, the comparison of treatment arms was restricted to only first recurrences and CBC. In terms of this endpoint the treatment difference was nonsignificant (HR=1.21, p=0.31), although the trend was still suggestive of a disadvantage for continued tamoxifen.

Table 1. B-14 5-year re-randomization: sites and rates of first events

	Placebo (569)			Tamoxifen (583)			Placebo vs. Tamoxifen		
	No. Events	%	Rate*	No. Events	%	Rate*	Rate-Ratio	95% CI	*p* Value
All breast cancer recurrences	34	6.0	8.9	47	8.1	12.5	1.4	0.9-2.2	
Local-regional	17	3.0	4.4	21	3.6	5.6	1.3	0.6-2.6	
Distant	17	3.0	4.4	26	4.5	6.9	1.6	0.8-3.1	
Second primary cancer	54	9.5	14.1	63	10.8	16.7	1.2	0.8-1.7	
Contralateral breast	20	3.5	5.2	17	2.9	4.5	0.9	0.4-1.7	
Endometrial	6	1.1	1.6	12	2.1	3.2	2.0	0.7-6.6	
Other	28	4.9	7.3	34	5.8	9.0	1.2	0.7-2.1	
Death prior to recurrence or second primary	18	3.2	4.7	27	4.6	7.2	1.5	0.8-2.9	
All events	106	18.6	27.6	137	23.5	36.3	1.3	1.0-1.7	0.03

* Average annual rate per 1,000 patients.

The NSABP data are compared to the Scottish and ECOG data in table 2. Findings to date from the Scottish trial are similar to those of B-14. A nonsignificant detriment was reported in the analysis of time to first recurrence, CBC, or death (HR=1.27, 95 percent CI 0.87–1.85) as well as overall survival (40 deaths versus 48). As in the NSABP trial, there were more endometrial cancers in those patients receiving tamoxifen. The published results from ECOG 4181/5181 are somewhat more positive. A nonsignificant advantage was seen for extended tamoxifen in terms of time to first recurrence or CBC (23 versus 15 events; recurrence-free survival at 5 years after re-randomization was 85 percent for those continuing tamoxifen versus 73 percent for those stopping at 5 years, p=0.10). In a secondary analysis restricted to patients who were ER-positive, this comparison became significant (22 versus 12 events, p=0.014). There was, however, no evidence of any survival benefit for continued tamoxifen (10 deaths in patients receiving 5 years of treatment versus 14 among patients receiving extended tamoxifen, p=0.52).

Table 2. Trials comparing 5 years of tamoxifen to longer durations

	NSABP B-14		Scottish Trial		ECOG 4181/5181	
	5 years T	Extended T	5 years T	Extended T	5 years T	Extended T
Number of patients	569	583	169	173	93	100
Number of recurrences + contralateral second primaries	54	64	28	38	23 (22*)	15 (12*)
Number of endometrial second primary cancers	6	12	1	4	1	0
Number of other second primary cancers	28	34	9	9	3	3
Number of deaths from all causes	39	57	40	48	10	14
Median followup after re-randomization	6.75 years		6.2 years		5.6 years	

* ( ) = number of recurrences or contralateral breast cancer among ER-positive patients.

In aggregate, there have been more reported recurrences and CBCs (117 versus 105) and deaths (119 versus 89) in patients randomized to continue tamoxifen than to those who stopped treatment. The apparent difference in the results of the ECOG trial and the other two studies may be due to chance (a crude heterogeneity test for between-trial differences based on recurrence counts is suggestive but not significant, p=0.09). Alternatively, it has been suggested that the optimal duration of treatment may differ for node-negative and node-positive patients (Tormey, Gray, Falkson, 1996). This may be so even if the risk reduction associated with breast cancer was independent of nodal status (as suggested by the EBCTCG overview data), since the recurrence rate in node-negative patients is considerably less than that in node-positive patients, even after 5 disease-free years (Tormey, Gray, Falkson, 1996). Long-term treatment with tamoxifen is associated with certain serious risks, most notably thromboembolic disease, endometrial cancer, and, possibly, stroke (EBCTCG, 1998; Fisher, Costantino, Redmond, et al.,

1994; Fisher, Costantino, Wickerham, et al., 1998). Therefore, even if it could be demonstrated that continued tamoxifen were efficacious, its risk/benefit ratio for node-negative women would be higher than for node-positive women (and higher for older women compared to younger).

Active Trials Testing Durations Beyond 5 Years

Both the aTTom (CRC Trials Unit, no date) and the ATLAS (Clinical Trials Service Unit, 1995) trials are now randomizing patients after 5 years of successful treatment with tamoxifen, either to stop the treatment or to continue it for an additional 5 years (Peto, personal communication). There are also three currently active trials in which hormone-responsive postmenopausal patients who have been successfully treated with tamoxifen for about 5 years are randomized to receive an additional 2 to 5 years of treatment with an aromatase inhibitor or a placebo. These include NCIC/EORTC/IBCSG/NCCTG/ECOG/ SWOG/CALGB MA 17 (Piccart, Goldhirsch, no date) (letrozole); NSABP B-33 (NSABP, 2000) (exemestane); and ABCSG Study 6A (Piccart, Goldhirsch, no date) (anastrozole).

Conclusions

There is strong evidence that 5 years of tamoxifen is superior to 2 to 3 years, at least in terms of delaying recurrence. Results up to now from trials comparing 5 to more than 5 years fail to indicate an additional advantage for continued tamoxifen, but the evidence is insufficient to achieve a satisfactory level of consensus, and continued enrollment of properly consented patients in long-term tamoxifen trials is appropriate. Alternatively, patients who have remained disease-free for extended periods of time on tamoxifen should be strongly considered for participation in clinical trials of other hormonal interventions, including aromatase inhibitors or selective estrogen receptor modulators (SERMs). Outside a clinical trials setting, adjuvant treatment with tamoxifen should be limited to 5 years duration until such time as additional data become available to definitively resolve the issue of tamoxifen duration.

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Recent NSABP Adjuvant Studies in Primary (Stage One) Breast Cancer

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Data on the effects of adjuvant chemotherapy and endocrine therapy on breast cancer obtained from randomized trials conducted during the 1970s and early 1980s were evaluated at a consensus development conference convened by the National Institutes of Health (NIH) in 1985. The conference concluded that there was inadequate information to recommend therapy other than surgery for women with negative nodes (Consensus Conference, 1985).

By 1990, however, findings from trials conducted by the National Surgical Adjuvant Breast Project (NSABP) and by other investigators warranted a new conference to reconsider the treatment of early-stage breast cancer. Participants at the 1990 meeting concluded that "the rate of local and distant recurrence following local therapy for node-negative breast cancer is decreased by both adjuvant combination of cytotoxic chemotherapy and by adjuvant tamoxifen" (NIH Consensus Conference, 1991). The conference also concluded that patients with tumors equal to or less than 1 cm now had an excellent prognosis and did not require adjuvant therapy outside of clinical trials. The participants noted, however, that studies so far were not large enough, nor followup long enough, to estimate accurately the interactions between menopausal status or steroid receptor positivity and adjuvant therapy in node-negative patients. They also noted that there were too few patients with estrogen receptor (ER)-negative tumors to permit evaluating the benefit of treatment with tamoxifen, that the followup period had been too short to obtain meaningful data on the mortality of women with breast cancer, and that no information was available to aid in determining the effects of combination chemotherapy plus tamoxifen in node-negative breast cancer patients. In the years since the 1990 conference, information on these issues has been obtained from six NSABP trials involving a total of 11,620 node-negative patients with primary breast cancer.

Findings for Adjuvant Chemotherapy

In the NSABP B-13 trial, women with breast cancer were randomized to receive either surgery and no chemotherapy or surgery followed by 12 courses (1 year) of methotrexate (M) and sequentially administered fluorouracil (F), (M→F), followed by leucovorin (Fisher, Dignam, Mamounas, et al., 1992). Findings through more than 12 years of followup demonstrated that improvements in disease-free survival (DFS) and overall survival as a result of that form of chemotherapy, first reported after 5 years, had persisted (p=0.004 and 0.039, respectively). A second trial, B-19, was conducted to determine if the alkylating agent cyclophosphamide (C) contributed an additional benefit when administered along with methotrexate and fluourouracil (CMF). Over a 6-month period, patients received either six courses of M→F or six courses of CMF. Through an 8-year followup period, CMF produced greater DFS and overall survival advantages (p=0.0004 and p=0.039, respectively).

The NSABP subsequently initiated a B-23 study because of contradictory information about the propriety of using tamoxifen with chemotherapy, and because of uncertainty about the relative worth of doxorubicin (Adriamycin, A), cyclophosphamide, and CMF for treatment of breast cancer (Fisher, Anderson, Tan-Chiu, et al., in press). Women with breast cancer (n=2,008) were randomized to receive either CMF plus placebo, or CMF plus tamoxifen, or doxorubicin and cyclophosphamide plus placebo, or doxorubicin and cyclophosphamide plus tamoxifen. Six cycles of CMF were given over 6 months; four cycles of AC were administered over a period of 63 days. No significant differences in the rates of relapse-free survival (RFS), event-free survival (EFS), or overall survival were observed among the four groups through 5 years of followup, either for all patients (p=0.9, 0.8, and 0.8, respectively) or for those ≤49 or ≥50 years of age.

The study also demonstrated that CMF was more effective than M→F for women with ER-negative tumors. There were, however, no significant differences in outcome between women who received 6 months of CMF and those treated with 2 months of AC. No significant advantage over that achieved from chemotherapy alone was found when tamoxifen was given with either regimen.

Findings on Tamoxifen

NSABP B-14 was initiated in 1982 to determine the effectiveness of tamoxifen in breast cancer patients with negative nodes (Fisher, Dignam, Bryant, et al., 1996; Fisher, Dignam, Bryant, et al., in press). In 1989, a report on 5 years of followup on more than 2,800 randomized patients found a significant advantage from treatment with tamoxifen. The DFS and overall survival rates persisted for more than 12 years (p=0.000005 and 0.0013, respectively). The therapy was also associated with a significant reduction in contralateral and ipsilateral breast cancer, but no additional benefit was observed from administration of tamoxifen beyond 5 years. These benefits were obtained with a relatively low incidence of side effects.

NSABP B-20, a study that involved more than 2,300 women, was aimed at testing the hypothesis that the addition of either M→F or CMF to tamoxifen would result in a greater benefit than that which could be achieved with tamoxifen alone (Fisher, Dignam, Wolmark, et al., 1997). After 8 years, there continue to be significant disease-free survival and overall survival advantages from the use of tamoxifen plus chemotherapy (44 percent versus 77 percent, p=0.002, for DFS; and 92 percent versus 88 percent, p=0.018, for survival). The B-20 study found no subgroup of women with breast cancer who did not benefit from administration of CMF with tamoxifen.

Findings on Patients with Tumors Less Than or Equal to 1 Cm and 1.1 to 2 Cm

In an attempt to resolve uncertainty about prognosis and treatment for patients with negative nodes and either ER-negative or ER-positive tumors of ≤1 cm, data from women in five NSABP randomized trials were analyzed collectively (Fisher, Dignam, Tan-Chiu, et al., in press). The 8-year rates of recurrence-free survival (RFS) for women with ER-negative tumors of ≤1 cm treated with surgery alone or with surgery plus chemotherapy were 81 percent and 90 percent, respectively (p=0.06). Survival was similar in both groups (93 percent and 91 percent,

respectively; *p*=0.65). The RFS rates for women with tumors between 1.1 and 2.0 cm were 77 percent for surgery and 81 percent for surgery plus chemotherapy (*p*=0.11). Overall survival was 77 percent and 84 percent, respectively (*p*=0.01).

The 8-year RFS rate for women with ER-positive tumors treated with surgery alone was 86 percent, compared with 93 percent after tamoxifen (*p*=0.01). When both tamoxifen and chemotherapy were given, the RFS was 95 percent (*p*=0.07). The survival rates among women in these three treatment groups were 90 percent, 92 percent (*p*=0.41), and 97 percent (*p*=0.01), respectively. The RFS rate for women with tumors of 1.2 to 2.0 cm treated with surgery alone was 75 percent, and with tamoxifen 88 percent ($p < 0.001$). The RFS rate was greater after chemotherapy and tamoxifen (91 percent) than after tamoxifen administration alone (*p*=0.003). Overall survival was 83 percent after surgery, 88 percent after tamoxifen was given (*p*=0.001), and 93 percent after both tamoxifen and chemotherapy (*p*=0.002).

Conclusion: The prognosis for women with ER-negative or ER-positive tumors of ≤1 cm and negative nodes was somewhat better than the prognosis for women with tumors between 1.1 and 2.0 cm. The prognosis was not sufficiently favorable, however, to dismiss systemic therapy as a possible option for certain women with tumors of ≤1 cm. A cutoff point in the array of tumor sizes below 10 mm that would justify systemic therapy remains to be established.

Radiation and/or Tamoxifen after Lumpectomy for Tumors of £1 Cm

The first results obtained from NSABP B-06 raised the question of whether there are cohorts of women for whom radiation therapy might be replaced with tamoxifen. NSABP B-21 was conducted to address that issue. Women (n=1,009) were randomized to either tamoxifen alone, radiation plus placebo, or radiation plus tamoxifen. Recently reported results demonstrated a rate (1,000 patients per year) of local recurrence of 23.3 for women who received tamoxifen, 11.7 for those who received radiation plus placebo, and 3.4 for those who received radiation plus tamoxifen (Wolmark, Dignam, Margolese, et al., 2000).

Conclusion: Radiation and tamoxifen administered in combination prevent local recurrence to a greater extent than does radiation alone. Tamoxifen alone is inferior to radiation in preventing recurrence.

Comment

Although almost all of the NSABP studies have demonstrated a benefit from therapy, they have all engendered controversy with regard to their clinical application. As the prognosis for both treated and untreated cohorts of breast cancer patients becomes better, therapeutic decision-making becomes more difficult. The question arises as to whether some proportion of women in a cohort can be justifiably "written off" because it has been decided that the group's prognosis is sufficiently good to negate treatment of any of them despite evidence that some of them might benefit from a therapy of demonstrated efficacy. Many women with breast cancer die each year because they have received either inadequate treatment or no treatment at all. Many others die despite having received "effective" treatment. Under these complex circumstances, it

would be inappropriate to deny any woman the opportunity to receive therapy from which she might benefit.

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Who Should Not Get Tamoxifen?

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Tamoxifen is a selective estrogen receptor modulator (SERM) that demonstrates antiestrogenic effects in breast cancer cells and in vaginal mucosa, and estrogenic effects in bone, endometrium, and the liver. These dual effects suggest that women taking tamoxifen might benefit from the drug's inhibitory effects on the cancer as well as from its agonist effects to maintain bone density and to lower cholesterol. Adverse effects would be expected from the estrogen-like stimulation of the endometrium.

Clinical trials of tamoxifen were started more than 25 years ago. The drug has an established role in the treatment of estrogen receptor (ER)-positive metastatic breast cancer and in adjuvant therapy in patients with primary breast cancer, and an evolving role in treating ductal carcinoma in situ (DCIS) and in prevention of breast cancer.

Invasive Breast Cancer and Tamoxifen

Individual randomized clinical trials as well as meta-analysis of all adjuvant trials clearly demonstrate that 5 years of adjuvant tamoxifen reduces the risk of recurrence and reduces mortality of women with ER-positive early breast cancer (see table 1).

Table 1. Effects of 5 years of adjuvant tamoxifen in patients with ER-positive breast cancer

Age	% Reduction in Odds ± SD	
	Recurrence	Death
All patients	47 ± 3	26 ± 4
< 40 years	54 ± 13	52 ± 17
40 - 49 years	41± 10	22 ± 13
< 50 years	45 ± 8	32 ± 10
50 - 59 years	37 ± 6	11 ± 8
60 - 69 years	54 ± 5	33 ± 6
70+ years	54 ±13	34 ± 13

Note: Adapted from Early Breast Cancer Trialists' Collaborative Group (1998).

Reductions in recurrence and mortality are seen irrespective of age, with patients under 40 years of age benefiting as much as older patients so long as the tumor expresses ER. Overall, such patients have a 40 to 50 percent annual reduction in the odds of recurrence. Patients whose tumors are strongly ER-positive have a 60 percent proportional reduction in recurrence. In addition, there is a 50 percent reduction in the incidence of contralateral breast cancer in patients treated with adjuvant tamoxifen.

Despite the effects of tamoxifen on cholesterol, no reduction in cardiac mortality has been observed in meta-analysis of tamoxifen adjuvant trials. An increased incidence of well-differentiated endometrial cancer as a result of tamoxifen therapy has been documented, although the beneficial effects of tamoxifen on breast cancer far outweigh that adverse event.

An important question is whether patients with ER-negative tumors receive some benefit with tamoxifen adjuvant therapy, either in terms of reducing the risk of recurrence and death from their primary tumor or in terms of the ancillary benefits in relation to contralateral breast cancer, cholesterol, and bone density. The meta-analysis shows no recurrence or mortality benefit in patients whose tumors are ER-negative in either the presence or absence of chemotherapy (EBCTCG, 1998). Two recently reported but as yet unpublished adjuvant trials were prospectively designed to determine the benefits of tamoxifen in ER-negative patients. Intergroup trial 0102 randomized high-risk node-negative patients, both ER-positive and ER-negative, to chemotherapy alone (CMF or CAF) or chemotherapy plus 5 years of tamoxifen (Hutchins, Green, Ravdin, et al., 1998). That trial showed no overall benefit with tamoxifen in the ER-negative subset, with a trend toward an unfavorable outcome in the premenopausal group. Patients with ER-positive tumors received significant benefit.

The other study, NSABP B23, randomized ER-negative patients to chemotherapy alone or chemotherapy plus tamoxifen (Fisher, Anderson, Wolmark, et al., 2000). That trial also showed no benefit from the addition of tamoxifen.

Thus, neither the meta-analysis of all trials nor the two large randomized clinical trials prospectively designed to answer the question show a recurrence or survival benefit for adjuvant tamoxifen in the ER-negative subset. Nonetheless, many physicians prescribe tamoxifen for ER-negative patients because of its potential benefit in reducing contralateral breast cancer. Emerging data that will be presented at this conference, however, suggest that, in marked contrast to the R-positive subset, the incidence of contralateral breast cancer is not reduced by tamoxifen in patients with ER-negative primary tumors. Thus, on the basis of current data, there is no justification for the use of adjuvant tamoxifen in patients whose tumors are ER-negative.

Ductal Carcinoma In Situ (DCIS)

Trials are in progress evaluating the role of tamoxifen in patients with DCIS following mastectomy or breast conservation surgery. Trials on invasive breast cancer suggest that tamoxifen may reduce the risk of ipsalateral breast cancer recurrence in patients treated with breast preservation as well as reduce the incidence of contralateral breast cancer. Such patients have little risk of dying of distant recurrence from their initial breast cancer, and the use of tamoxifen in these patients might be viewed as chemoprevention, much like its use in patients

with increased breast cancer risk. One large randomized trial (NSABP B-24) has been completed, and early results have been published (Fisher, Dignam, Wolmark, et al., 2000). More than 1,800 women with DCIS with either positive or negative surgical margins were randomized to lumpectomy plus radiation or to lumpectomy plus radiation plus tamoxifen. Women in the tamoxifen arm had significantly fewer invasive and noninvasive breast cancers in the ipsalateral breast and also a reduction in contralateral breast cancer. Slightly more patients on tamoxifen developed venous thrombotic events, but there have been no treatment-related deaths. As expected, there was an increased rate of endometrial cancer in patients treated with tamoxifen. These data suggest that tamoxifen treatment can be considered in women treated with lumpectomy and radiation therapy to prevent both ipsalateral and contralateral invasive breast cancer. Tamoxifen would also be expected to reduce the incidence of contralateral breast cancer in patients treated by mastectomy, but the drug has not been studied definitively in this group. The role of ER status in predicting tamoxifen benefit in patients with DCIS has not been examined.

Prevention

Three randomized trials have addressed the role of tamoxifen in breast cancer prevention. One of these, the P-1 trial run by the NSABP and reported by Fisher and colleagues (Fisher, Costantino, Wickerham, et al., 1998) was a large double-blind randomized trial involving more than 13,000 women with an increased breast cancer risk receiving either placebo or tamoxifen for 5 years. That trial showed a 50 percent reduction in the incidence of breast cancer after 3 to 4 years of followup. There was also a reduction in bone fractures, but no change in cardiac mortality. The incidence of endometrial cancer increased, as expected, but thus far there are no deaths from endometrial cancer in patients in the tamoxifen arm. A slight increase in the need for cataract surgery in women with preexisting cataracts and a slight increase in thromboembolic events were also reported. Similar data were observed in a trial using raloxifene for osteoporosis (Cummings, Eckert, Krueger, et al., 1999). However, the reduction in breast cancer incidence observed in the latter trial is considered less definitive, since it was a secondary endpoint. Nevertheless, data from that trial add weight to the evidence that SERM therapy reduces the incidence of breast cancer in women who do not yet manifest the disease.

Two other trials using tamoxifen in prevention have been reported (Powles, Eeles, Ashley, et al., 1998; Veronesi, Maisonneuve, Costa, et al., 1998). The trial by Powles and colleagues was a feasibility study randomizing more than 2,000 women who had an increased risk of breast cancer based on family history. Overall, the trial showed no significant reduction in breast cancer incidence, although there was a reduction in the number of ER-positive breast cancers. Interpretation of the evidence from that trial, however, suffers because of the concomitant use of estrogen replacement therapy in many of the women and by its smaller size and initial design as a pilot feasibility trial. The study by Veronesi and colleagues involved 5,000 women who had previously undergone hysterectomy. It showed no overall benefit for tamoxifen, although there was a trend toward reduction in ER-positive breast cancers. Interpretation of the data from that trial is also clouded by the use of hormone replacement therapy by some patients and from a high patient dropout rate.

The cumulative evidence at this time suggests that in high-risk women, 5 years of tamoxifen reduces the incidence of in situ and invasive breast cancer in both pre- and postmenopausal women. A risk-benefit analysis suggests that greater relative benefit will be observed in younger women (Gail, Costantine, Bryant, et al., 1999). Although many questions remain to be answered, tamoxifen can be considered for women meeting the criteria of eligibility for the
P-1 trial (Chlebowski, Collyar, Somerfield, et al., 1999). Women not meeting those criteria should not receive tamoxifen until the data clearly demonstrate a favorable risk-benefit ratio.

Conclusion and Future Direction

There are no data to support the use of tamoxifen in patients with ER-negative invasive breast cancer. Tamoxifen can be considered in certain subsets of women with DCIS and in women at increased risk for breast cancer. Women with an average risk for developing breast cancer should not receive tamoxifen at this time. Future studies should address the optimal duration of tamoxifen for treatment and prevention, the value of ER expression in predicting the tamoxifen benefit for patients with ductal carcinoma in situ, the risk-benefit profile obtained by longer followup of patients in prevention trials, health economic outcomes, the role of tamoxifen in tumor prevention in women with hereditary susceptibility to cancer, and trials of other SERMs with a more favorable therapeutic ratio.

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Hormonal Ablation

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Ovarian ablation was the first form of adjuvant systemic therapy used in premenopausal women with early-stage breast cancer. A 1995 meta-analysis summarized results from 12 of the 13 randomized studies that assessed ovarian ablation by irradiation or surgery; these trials all began before 1980 (EBCTCG, 1996). Because menopausal status was not uniform across these studies, analysis was directed at the 2,102 women in the studies under the age of 50, most of whom were likely to be premenopausal. Ovarian ablation led to a 25 $\pm$ 7 percent reduction in the annual odds of recurrence, and a 24 $\pm$ 7 percent reduction in the annual odds of death, for women who underwent ovarian ablation in the absence of chemotherapy. The benefit appeared significant for both node-negative and node-positive women. There was a trend for greater efficacy of ablation in women with estrogen receptor-positive tumors, although this was only assessed in 4 of the 12 trials, all of which included chemotherapy. The benefit was less pronounced for women who were randomized to ovarian ablation in the presence of chemotherapy (10 $\pm$ 9 percent and 8 $\pm$ 10 percent, respectively). It is expected that this analysis will be updated and expanded with 20 years of followup later this year.

More recent trials have expanded and refined our knowledge in this field. They have focused largely on two questions: What are the relative effects of adjuvant chemotherapy and ovarian ablation with or without tamoxifen in premenopausal women? Does ovarian ablation have additional benefit in young women who have received adjuvant chemotherapy? Key features of some of these newer trials are careful (but variable) definition of premenopausal status, enrollment of women with steroid receptor-positive tumors, and the use of luteinizing hormone-releasing hormone (LH-RH) agonists to effect a temporary “chemical” castration.

Two trials have compared adjuvant ovarian ablation to cyclophosphamide, methotrexate, fluorouracil (CMF) chemotherapy. The Scottish/ICRF trial of 332 premenopausal women with node-positive breast cancer showed no difference in event-free or overall survival after a maximum followup of 12 years (SCTBG, 1993). Estrogen receptor (ER) assays were available for 270 tumors; retrospective analyses suggested that oophorectomy was associated with improved survival in patients with ER concentrations $\geq$20 fmol/mg protein, while six months of oral CMF was more beneficial for patients with ER <20 fmol/mg protein. A second trial assessed ovarian ablation and nine cycles of IV CMF in 732 women with hormone receptor-positive breast cancer that involved lymph nodes or that measured more than 5 cm(Ejlertsen, Dombernowsky, Mouridsen, et al., 1999). The 5-year disease-free survival (DFS) rate was 67 percent with ovarian ablation and 66 percent with CMF; corresponding survival rates were 78 percent and 82 percent respectively (nonsignificant). Amenorrhea occurred in 68 percent of the patients receiving CMF. Together, these trials suggest that oophorectomy and CMF chemotherapy have similar effects in women with node-positive breast cancer. Results of a third trial (ZEBRA) that compared CMF with goserelin, a LH-RH agonist, in women with early-stage breast cancer of any receptor type should be available at the time of the consensus conference. If

consistent, these data will suggest that the efficacy of adjuvant CMF may be mediated at least in part by its ability to ablate ovarian function, leading to a state of estrogen withdrawal.

The concept of combined endocrine therapy has also been tested in two trials using CMF. The GROCTA 02 study compared oral CMF with 2 years of goserelin and 5 years of tamoxifen in 244 women with node-positive ER-positive breast cancer (Boccardo, Rubagotti, Amoroso, et al., 1998). Five-year disease-free survival was 69 percent for CMF and 72 percent for goserelin-tamoxifen (not significant), and survival was identical at 87 percent.

A larger trial of similar design was conducted by the Austrian Breast Cancer Study Group [ABCSG] (Jakesz, Hausmaninger, Samonigg, et al., 1999). ABCSG compared IV CMF for six cycles with goserelin for 3 years, and tamoxifen for 5 years, in 1,045 women with stage I and II steroid receptor-positive breast cancer. At a median followup of 42 months, combination endocrine therapy showed a significantly improved recurrence-free survival (RFS) compared with CMF (p=0.02), without an impact on survival. In the CMF group, those women who developed amenorrhea had significantly better RFS and survival than those who did not. A third trial compared six cycles of IV FEC (an anthracycline-containing regimen) with 3 years of tamoxifen and triptoreline (another LH-RH agonist) in 333 premenopausal women with hormone receptor-positive breast cancer involving 1 to 3 nodes (Roche, Kerbrat, Bonneterre, et al., 2000). With median followup of 54 months, disease-free survival and overall survival were 92 percent and 97 percent, respectively, for endocrine therapy, and 81 percent and 93 percent for FEC; these differences are not significant. FEC induced amenorrhea in 42 percent of patients. Thus, these three trials suggest that combined endocrine therapy has effects similar to those of adjuvant chemotherapy, although it is not likely that any of these trials had the statistical power to document true equivalence.

Adjuvant chemotherapy is a routine part of care for many women with node-positive breast cancer. Thus, a second question is whether the use of ovarian ablation adds to the benefits of adjuvant chemotherapy. This question was addressed in INT 0101, a trial of chemohormonal therapy in 1,503 premenopausal women with node-positive, receptor-positive breast cancer (Davidson, O'Neill, Vukov, et al., 1999). The trial compared three treatment arms: six cycles of oral CAF, six cycles of CAF followed by 5 years of goserelin (CAF→Z), and six cycles of oral CAF followed by 5 years of goserelin and tamoxifen (CAF→ZT). The 7-year disease-free survival rates were 58 percent for CAF, 64 percent for CAF→Z, and 73 percent for CAF→ZT. Comparison of CAF→ZT with CAF→Z showed a significant disease-free survival rate advantage with the addition of tamoxifen (p=0.0025), while comparison of CAF→Z with CAF showed no disease-free survival rate advantage for the addition of goserelin (p=0.0955). Survival at 7 years was similar for all three arms: 77 percent for CAF, 78 percent for CAF→Z, and 80 percent for CAF→ZT. Final analysis of the impact of amenorrhea, patient age, and serum hormone levels on clinical outcome is in progress.

The ZIPP trial also permitted assessment of the effects of ovarian ablation in the context of other adjuvant therapy (Baum, 1999). That study combined results from four trial groups that used a common 2x2 design to evaluate tamoxifen for 2 years, goserelin for 2 years, tamoxifen and goserelin for 2 years, and no endocrine therapy, in 2,631 premenopausal women with early-stage breast cancer of any steroid receptor type (56 percent node-negative). Elective adjuvant chemotherapy was permitted in selected patients according to predetermined plans and was given

to 43 percent of the participants. At a median followup of 4.2 years, there was a statistically significant 23 percent reduction in first events in women who received goserelin (first events in 20 percent of patients with goserelin and 25 percent of patients without goserelin, p=0.001). The benefit was less pronounced in patients who received concurrent adjuvant tamoxifen or chemotherapy. There is no significant effect on survival at the present time (p=0.12).

Available data suggest that both adjuvant ovarian ablation with or without tamoxifen and CMF chemotherapy have similar benefits for premenopausal women with early-stage breast cancer. Thus, ovarian ablation (± tamoxifen) appears to be a reasonable alternative to CMF chemotherapy for selected women with receptor-positive breast cancer. It appears unlikely, however, that ovarian ablation has a benefit for women with receptor-negative tumors.

A number of questions remain to be answered. These include (1) the importance of amenorrhea as a determinant of outcome for premenopausal women with early-stage breast cancer; (2) the optimal duration of ovarian ablation if an LH-RH agonist is employed; (3) the relative efficacy of ovarian ablation and other types of adjuvant chemotherapy (e.g. CAF, AC, or AC followed by paclitaxel); (4) the additional value of ovarian ablation after chemotherapy, particularly for women who remain premenopausal after adjuvant chemotherapy; and (5) the value of combined hormone therapy.

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Overview: Progress in Systemic Chemotherapy of Primary Breast Cancer

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Improved understanding of the natural history of breast cancer led to the systematic evaluation of adjuvant chemotherapy. Progress has been based on knowledge derived from randomized clinical trials (EBCTCG, 1998). The following paragraphs report salient points of progress.

Adjuvant chemotherapy significantly reduces the annual odds of recurrence and death for patients with primary breast cancer. The relative reduction in risk is similar regardless of initial tumor burden or prognostic category. The magnitude of benefit is greater in women less than 50 years of age than in those at or older than 50. Combination chemotherapy with two or more agents is more effective than single-agent therapy.

The optimal duration of chemotherapy has also been addressed in prospective clinical trials (Henderson, Gelman, Harris, et al., 1986). Prolonged chemotherapy for 4 to 6 months is superior to a single perioperative dose. The administration of chemotherapy for more than 6 months, utilizing the same cytotoxic regimen, is not superior to 6 months or less.

The initial clinical trials used cyclophosphamide-methotrexate-5-flourouricil (CMF) and related regimens. The second generation clinical trials of adjuvant chemotherapy evaluated the role of anthracyclines in the management of micrometastases (EBCTCG, 1998). Several individual randomized trials and the Oxford overview of randomized trials demonstrated that anthracycline-containing regimens were superior to nonanthracycline-containing regimens, and that the addition of an anthracycline resulted in an incremental reduction in odds of recurrence and death (EBCTCG, 1998; Levine, Bramwell, Pritchard, et al., 1998). Although the incremental benefit of an anthracycline-containing regimen was smaller in magnitude than that of polychemotherapy in relation to no adjuvant treatment, it became evident in retrospect that several of the randomized trials utilized suboptimal doses of anthracyclines. More recent information suggests that anthracycline-containing regimens may be particularly effective in patients with tumors that overexpress the HER-2/neu oncogene (Paik, Bryant, Park, et al., 1998; Ravdin, Green, Albain, et al., 1998). These same studies suggest that the utility of anthracyclines would be marginal (compared to nonanthracycline-containing regimens) for patients whose primary breast cancer had a normal expression of HER-2/neu. These data and correlations, however, must be confirmed prospectively.

Over the past 20 years, much energy and resources have been expended on the evaluation of dose-intensive chemotherapy in the adjuvant setting. The results of multiple clinical trials suggest that there is a threshold effect for several of the commonly used regimens and that doses that fall below such a threshold result in less or no benefit. However, there is no clinical evidence at this point that continued increase in dose intensity above the threshold dose results in improved outcome (Hortobagyi, 1999; Rahman, Hortobagyi, Buzdar, et al., 1998). The

preliminary results of randomized clinical trials exploring the value of high-dose chemotherapy and autologous stem cell support in the adjuvant setting have not demonstrated a reproducible and significant clinical benefit superior to that of standard dose chemotherapy (Hortobagyi, 1999).

The role and value of adjuvant hormonal therapy is reviewed elsewhere. The addition of chemotherapy to hormonal therapy for patients with estrogen receptor-positive tumors has been shown to result in incremental reductions in odds of recurrence and death for both pre- and postmenopausal patients. Similar results have been found for patients with node-positive and node-negative breast cancer.

Recently published results suggest that the addition of paclitaxel to an anthracycline cyclophosphamide-containing regimen results in a greater reduction in odds of recurrence and death than those obtained with the anthracycline regimen alone (Henderson, Berry, Demetri, et al., 1998).

Several randomized trials have produced results suggesting that the introduction of a second noncross-resistant regimen after a course of primary adjuvant chemotherapy would improve the therapeutic results (Perloff, Norton, Korzun, et al., 1996). The trial with paclitaxel following the anthracycline cyclophosphamide regimen falls in this category, and continued evaluation of sequential, noncross-resistant regimens should produce results of great interest.

Another important topic in designing optimal adjuvant regimens is the timing of systemic chemotherapy. The majority of the data (on which current management is based) were derived from prospective randomized trials comparing surgery alone with surgery followed by postoperative adjuvant chemotherapy. More recently, preoperative chemotherapy (utilizing regimens similar to those employed in postoperative adjuvant treatment) has been evaluated in several prospective randomized trials (Fisher, Brown, Mamounas, et al., 1997; Kuerer, Newman, Smith, et al., 1999). It is apparent that combination chemotherapy results in objective regression in the great majority of tumors. This reduction in tumor size increases the proportion of patients who are candidates for breast-conserving surgery and also results in substantial downstaging in the breast and regional lymph nodes. Not surprisingly, preoperative chemotherapy does not confer improved survival when compared to the same regimen used postoperatively. However, additional benefits—including preoperative evaluation of sensitivity to chemotherapy—are associated with preoperative chemotherapy (Fisher, Brown, Mamounas, et al., 1997; Kuerer, Newman, Smith, et al., 1999). Ongoing trials will determine whether this information can be translated into improved therapeutic results by the timely introduction of noncross-resistant systemic therapy.

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Is Her-2/neu a Predictor of Anthracycline Utility in Adjuvant Therapy? A Qualified Yes.

Peter M. Ravdin, M.D., Ph.D.

The use of Her-2/neu overexpression to select patients who might benefit from adjuvant anthracyclines was first suggested in 1994. Now, 6 years later, the use of Her-2 to guide adjuvant chemotherapy still remains a matter of controversy. Nonetheless, there is some evidence that Her-2 can and should be used for this purpose. It is therefore worthwhile to examine the reasons why this evidence has fallen short of being convincing, and why Her-2 overexpression has not yet become a standard method to help select adjuvant therapy.

The principal shortcoming of the evidence is that none of the adjuvant trials whose results have been used to examine this question were designed for that purpose. They were designed to answer treatment questions only. Moreover, a two-arm trial becomes a four-arm trial when stratified by a biomarker, and Her-2 is a particularly nettlesome biomarker because it is overexpressed in only about 20 to 30 percent of cases. As a result, the overexpressing subset is generally small. That weakens the power of the studies.

How big would an ideal trial be? Estimating the sample size as a two-arm trial in node-positive patients with adjuvant anthracycline-based therapy being twice as effective in Her-2 overexpressing patients, and about 20 to 30 percent of the patients overexpressing Her-2, the number of patients required for the trial would be 2,000 to 3,000. Given that the largest reported studies dealing with Her-2 in adjuvant therapy involved about 1,000 patients, it is clear that most of what we know is based on underpowered studies, many of them with a power of 0.50 or less.

This would seem to be an ideal area for a meta-analysis, but that would be somewhat problematic because of another feature of the studies pertaining to Her-2. Unlike treatment trials with well-defined standardized endpoints (disease-free survival [DFS] and overall survival [OS]), the endpoints (stratification) for using Her-2 are not well defined. There was no uniformity in the trials in how Her-2 testing was done; a number of different systems (based on percentage of cells staining, stain intensity, and stain cellular location) were used to interpret whether Her-2 was overexpressed by a given tumor. Thus, some of the variation in the results of the studies may be due to simple methodological differences.

It has been argued that the mechanism by which Her-2 overexpression leads to a sensitivity to adjuvant anthracyclines is unclear. The mechanism is indeed rather obscure, with some preclinical systems suggesting that it exists, and some finding just the opposite—that Her-2 overexpression may confer resistance to anthracyclines. Adding to the confusion is the fact that Her-2 overexpression in patients with metastatic disease is not unequivocally associated with response to anthracyclines, and in some instances seems to have been associated with resistance (Vincent-Salomon, Carton, Freneaux, et al. 2000; Sjostrom, Krajewski, Franssila, et al. 1998; Jarvinen, Holli, Kuukasjarvi, et al. 1998). These studies of metastatic disease were generally small, however, and may be confounded by the biology of Her-2, which in general is associated

with unfavorable features (such as faster cell proliferation) that may mask or counterbalance the benefits of higher efficacy.

What is clear is that arguments for the use of Her-2 in selecting adjuvant chemotherapy are not as simple as the arguments for use of the estrogen receptor (ER) in selecting adjuvant endocrine therapy. In the case of the estrogen receptor, there are very clear molecular correlates, preclinical system evidence, and supportive evidence in metastatic disease for use of the ER. In addition, the ratio of response rates in metastatic disease based on the estrogen receptor's presence or absence is 10:1. It is clear from the data that the usefulness of Her-2 in assessing the benefit of anthracyclines will be more modest.

Having conceded these points, it is important to review how this HER-2 hypothesis was developed and the consistency of the clinical trial evidence that supports it. The initial report was from the CALGB, which analyzed a trial in which node-positive breast cancer patients were randomized between one of three different dose intensities of cyclophosphamide and Adriamycin. Only in the Her-2 overexpressing patients did the dose make a difference, and thus it appeared that Her-2 overexpression identified a subset of patients who particularly benefited from anthracyclines (Muss, Thor, Berry, et al., 1994).

The CALGB's own attempt to replicate those results has been controversial. The second CALGB study used patients from the second half of the trial, but the benefit was not as clear and did not reach statistical significance. But by using elaborate statistical techniques and combining data from the two halves of the study, the investigators were again able to demonstrate that Her-2 overexpression identified a subset of patients with anthracycline sensitivity (Thor, Berry, Budman, et al., 1998). Those studies have inspired a number of other tests of whether Her-2 overexpression identified a subset of patients who were particularly likely to benefit from adjuvant therapy.

The first of those studies used results from NSABP B-11. In that trial, patients were randomized between melphalan and 5-fluorouracil (PF) or the same drugs plus doxorubicin (PAF). Patients overexpressing Her-2 were the only subset for whom PAF resulted in a statistically significant risk reduction, despite the fact that the subset was only about half the size of the subset with low (normal) Her-2 expression. The test for a statistically significant difference in risk reduction between the subsets reached statistical significance for DFS and showed a strong trend as a predictor of OS (Paik, Bryant, Park, et al., 2000).

A second NSABP study extended these observations. In this study, based on material from NSABP B-15, tumor samples from the arms receiving CMF or CA were analyzed. Again, the hazards of relapse and death were more strongly reduced in the patient subset overexpressing Her-2 and receiving CA. The test for interaction did not reach statistical significance, but a trend toward greater benefit was seen (Paik, Bryant, Tan-Chiu, et al., 1998).

The same trends were seen in S8814, where postmenopausal ER+ patients were randomized between tamoxifen and CAF plus tamoxifen (a 3 to 10 randomization). Again, chemoendocrine therapy was superior only in the Her-2 overexpressing patients, but once again the difference did not reach statistical significance (Ravdin, Green, Albain, et al., 1998).

The last large study to provide data for the present review was EORTC 10854, in which node-negative premenopausal women were randomized to one perioperative (immediately postoperative) cycle of CAF or to no further adjuvant therapy. At 4 years of followup, a reduction in the hazard of relapse was seen in both the Her-2 positive and Her-2 negative subsets, but appeared larger in the Her-2 positive subset. Here too, the difference did not reach statistical significance (Clahsen, van de Velde, Duval, et al., 1998).

In summary, a pattern is emerging in adjuvant studies showing that the Her-2 positive (overexpressing) subset derives greater benefit from adjuvant therapy than the Her-2 negative subset. The low statistical power of the four studies makes this effect difficult to demonstrate statistically, but the studies do suggest that such an interaction exists.

Table 1. Trials with retrospective assessment of impact of Her-2*

				Her-2 +		Her-2 –	
				DFS	**OS**	**DFS**	**OS**
NSABP B-11	PF	vs.	PAF				
N=	316		322				
Hazards				0.60	0.66	0.96	0.90
p=value				0.001	0.01	0.74	0.47
Interaction				***0.02***	***0.15***		
NSABP B-15	CMF	vs.	CA				
N=	666		689				
Hazards				0.84	0.82	1.08	1.06
p=value				0.15	0.14	0.84	0.51
Interaction				***0.19***	***0.11***		
S8814	Tam	vs.	CAF Tam				
N=	173		572				
At 5 years				52/67	60/80	80/79	86/88
p=value				0.03	0.02	0.94	0.83
Interaction				***0.22***	***0.23***		
EORTC 10854	Control	vs.	FAC				
N=	210		231				
Hazards				0.44		0.64	
p=value				0.17		0.05	
Interaction				–		–	

* Smaller studies have been reported in abstract form, some of which have supported the concept (Vera, Albanell, Lirola, et al., 1998) or else have involved complex multisubset analyses that make it difficult to interpret the results (DiLeo, Larsimon, Beauduni, et al., 1998). The table compares the results of the larger studies discussed in this review.

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Is HER-2/neu a Predictor of Anthracycline Utility? No.

George W. Sledge, Jr., M.D.

HER-2/neu is important in the natural history of breast cancer. This importance derives from HER-2/neu's role in tumor growth, invasion, and metastasis (the clinical summation of which is its role as a prognostic factor in early-stage breast cancer) as well as its role as a predictor of response to trastuzumab (Herceptin monoclonal antibody). These roles for HER-2/neu seem firmly established.

Three recent American cooperative group trials have suggested that patients receiving adriamycin are the most likely to benefit if their tumors overexpress the HER-2/neu glycoprotein. This role of HER-2/neu, as a predictor of anthracycline utility seems promising, and if confirmed clearly would be of importance. But to what extent should we accept the data presented to date?

Problems in Positive Trials

Three trials have reported positive results (Paik, Bryant, Park, et al., 1998; Thor, Berry, Budman, et al., 1998; Ravdin, Green, Albain, et al., 1998). Individually and collectively, however, these trials suffer from potential and actual flaws. All data presented to date utilize immunohistochemical techniques (IHC), and such techniques are well known to suffer from methodological flaws. Even in good hands, the correlation of these techniques with the "gold standard" of fluorescence in situ hybridization (FISH) is only about 80 percent. IHC techniques also have unknown correlations with each other, and all three studies used differing antibodies and techniques. In each case, tissue collection was retrospective. In one of the studies (Thor and colleagues), the antibody utilized was switched mid-study; in another (Paik and colleagues), the IHC technique was done on old slides rather than off paraffin-embedded tissue.

Leaving aside these potential methodological flaws, the analyses of the reported trials leave something to be desired. All three involved retrospective analyses and should therefore be viewed as hypothesis-generating rather than as proof-of-principle studies. In the Cancer and Leukemia Group B (CALGB) trial, an initial analysis reported positive results, a second analysis with a somewhat larger number of patients failed to reach statistical significance, and a third analysis combining the two was once again positive. The data reported by SWOG involved subset analyses involving a truly small number of patients, with broad confidence intervals. Tests for interaction did not reach statistical significance in any of the three trials.

Finally, what are we to make of comparing the available trials? In the first trial reported (CALGB), "high-dose" anthracycline-based therapy was superior to "low-dose" anthracycline-based therapy. The low-dose arm of the CALGB trial, however, utilized the same dose intensity employed in the standard AC arm of NSABP B-11. Are we to believe that the magnitude of

difference between AC and CMF in the NSABP trial is equal to the magnitude of difference between that same dose and twice the dose of adriamycin? That seems unlikely.

Problems With Consistency

Though most doxorubicin-based adjuvant trials have reported positive results, at least one epirubicin-based analysis reported no differential benefit for HER-2 positivity (Untch, Konecny, Lebeau, et al., 1998). That study compared a standard-dose epirubicin/cyclophosphamide combination with a dose-intense epirubicin/cyclophosphamide regimen. Only in the HER-2 negative subgroup was there a benefit for the dose-intense regimen, a result that contrasts strikingly with the CALGB results. Given that epirubicin is at least as beneficial in the adjuvant setting as doxorubicin, how could one explain the absence of an HER-2 related benefit?

Similarly, Colozza, Gori, Mosconi, et al. (1999) evaluated the effect of HER-2 status in a trial comparing epirubicin with CMF adjuvant chemotherapy in patients with Stage I or II breast cancer. With a median followup of 5.6 years and 266 patients available for HER-2 status, epirubicin treatment had no significant impact on the outcome of patients with HER-2 positive tumors.

One would expect a consistency of effect across all stages of breast cancer if the HER-2 relationship were real. We would not expect a predictive factor to have a benefit in Stage II breast cancer but not in Stage III or IV breast cancer, yet this is what we are asked to accept for the HER-2/doxorubicin interaction. Numerous trials have examined the effect of HER-2 overexpression on response to preoperative or metastatic anthracycline-based regimens. These trials (summarized in table 1) are inconsistent in their results, and generally fail to demonstrate a positive relation. Although the number of patients entered in these trials was small relative to the numbers of those in adjuvant trials, the number of events is large, since virtually every patient entered was measurable for response.

Table 1. Effect of HER-2/neu overexpression on response to anthracycline-based pre-operative or metastatic chemotherapy regimens

Author	Stage	N	Effect
Kling	III	32	None
MacGrogan	II-III	126	None
Vincent-Solomon	II-III	54	None
Zapf	III	46	None
Petit	II-III	79	Negative (low dose) Positive (dose intensification)
Dieras	II	89	Positive
Niskonen	IV	127	None
Jarvinen	IV	55	Negative
Stender	IV		None

Biologic Problems

If HER-2 overexpression conferred sensitivity to doxorubicin in the clinic, one would expect that a similar effect might be seen in the laboratory. Pegram and colleagues tested this hypothesis by transfecting four breast cancer cell lines with HER-2 and then exposing them to doxorubicin in vitro. No alteration in chemosensitivity was observed in any of the transfected breast cancer cell lines versus the parent cell lines, nor in a related in vivo nude mouse xenograft model (Pegram, Finn, Arzoo, et al., 1997).

Problems With Extrapolation

The problem with accepting the results seen in the available adjuvant trials mirrors the problem with HER-2 testing in general. Immunohistochemical analysis of HER-2 is only imperfectly correlated with fluorescence in situ hybridization (FISH), and is subject to interobserver reproducibility problems, problems with technique, and problems with tissue preservation. None of the current trials used the same immunohistochemical techniques. How then can we extrapolate the results to clinically available testing kits?

Similarly, proponents of the HER-2/doxorubicin link need to follow through on the logical conclusions of this linkage. Two-thirds to three-quarters of breast cancer patients are HER-2 negative. The same studies suggesting a benefit for doxorubicin in HER-2 positive patients show a lack of added benefit in HER-2 negative patients. Given the overview demonstration of benefit for anthracycline-based regimens in the adjuvant setting, are we really confident that doxorubicin can be omitted in HER-2 negative patients?

Conclusion

HER-2/neu testing has many real benefits. These benefits should not blind us to the real concerns surrounding the use of HER-2 as a therapeutic predictor for anthracyclines. We currently lack a solid biologic basis for the proposed linkage. The available positive studies have real uncertainties. There are studies contradicting the linkage in the adjuvant, neo-adjuvant, and metastatic settings. The cumulative weight of these concerns calls the hypothesis into question. Until more solid data emerges, HER-2 should not be accepted as a predictor.

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Adjuvant Chemotherapy: Taxanes–the "Pro" Position

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Following publication of the first paclitaxel trials for patients with metastatic breast cancer in 1993, the taxanes were quickly incorporated into standard practice because they are less cross-resistant with anthracyclines than most other drugs (Sledge, Neuberg, Ingle, et al., 1997). The Cancer and Leukemia Group B (CALGB) and the Intergroup had planned a randomized trial evaluating the importance of doxorubicin dose in an adjuvant chemotherapy regimen, but because of the compelling nature of the paclitaxel data this trial was enlarged, and a 3x2 design was employed so that two questions could be addressed. Between May 1, 1994, and April 15, 1997, some 3,170 women with operable breast cancer and involved lymph nodes were treated with cyclophosphamide (C) (600 mg/M), and randomized to one of three doses of doxorubicin (A) (60, 75, or 90 mg/M^2). Four cycles of CA were given to all patients at 3-week intervals. G-CSF was routinely given to the patients receiving the 90 mg/M^2 dose.

On the basis of their initial randomization, patients either discontinued all adjuvant chemotherapy after completion of CA or received 4 cycles of paclitaxel (T) (175 mg/M^2). Tamoxifen, 20 mg daily for 5 years, was offered to all patients with hormone receptor-positive (ER and/or PgR) tumors. All patients treated with breast-conserving surgery were also treated with radiotherapy to the breast. Adjuvant radiotherapy was given to patients treated with mastectomy at the discretion of the primary physician. Radiotherapy was given after all chemotherapy was completed (after 3 months for those randomized to CA alone, and after 6 months for those randomized to CA+T).

The first analysis of this trial was completed after 453 events (recurrence or death) and a median followup of 20 months (Henderson, Berry, Demetri, et al., 1998). The second analysis was completed after 624 events and a median followup of 30 months. There were no differences in the main endpoints between the first and second analysis. A third analysis will be conducted, as originally planned in the protocol design, after 900 events. An independent data safety monitoring board performed group sequential monitoring and determined the date of the first presentation of these data.

The entry characteristics of the patients were balanced among the three study arms; 62 percent of the patients were premenopausal; 66 percent had receptor-positive (ER and/or PgR) tumors; 46 percent had 1 to 3 involved axillary nodes, 42 percent had 4 to 9 involved axillary nodes, and 12 percent had 10 involved axillary nodes. Thirty percent of the patients chose breast-conserving surgery as their primary treatment.

There were no differences in outcome related to doxorubicin dose. However, the hazard reductions from adding paclitaxel to CA were 22 percent for recurrence ($p = 0.0022$) and 26 percent for death ($p = 0.0065$). At 3 years the disease-free survival rate was 73 percent after CA alone and 77 percent after CA plus paclitaxel; overall survival was 84 percent after CA alone and 87 percent after CA plus paclitaxel. There was no evidence of an interaction between doxorubicin and paclitaxel, and adding paclitaxel was equally beneficial among those initially given 60, 75, or 90 mg/M^2 of doxorubicin. The benefits from adding paclitaxel were not significantly different in patient subsets defined by tumor size, number of positive lymph nodes, or menopausal status. These were the only subset analyses anticipated in the original protocol.

The most recent Oxford overview of adjuvant therapy trials suggested that chemotherapy was generally less effective among women who had hormone receptor-positive tumors and/or had been treated with adjuvant tamoxifen. Reductions in annual odds of recurrence or death from the use of chemotherapy were substantially (but not always significantly) smaller among receptor-positive or tamoxifen-treated patients regardless of patient age (EBCTCG, 1998). Although a subset analysis based on either receptor status or the use of tamoxifen was not planned in the original protocol for our trial, a post hoc analysis demonstrated a trend similar to that seen in the overview. The reduction in the hazard of recurrence was 8 percent and 32 percent, respectively, for those with receptor-positive and receptor-negative tumors. Almost all of the patients with receptor-positive tumors received adjuvant tamoxifen, and the differences in the effects of adding paclitaxel among those who did and did not receive tamoxifen is similar to the analysis of hormone receptor subsets. These differences in the effect of paclitaxel are not statistically significant, and when each subgroup is analyzed separately the effect of adding paclitaxel is not statistically significant in the receptor-positive or tamoxifen-treated groups.

When breast radiotherapy was given, it was initiated 3 months after surgery among those randomized to CA alone and 6 months after surgery among those on the CA+T arm of the trial. No significant differences in local control of disease were seen between the two arms of the study. In fact, there was a small trend towards better local control following CA+T, but the total number of local recurrences is still too small to draw firm conclusions about the effect, if any, of this delay.

The improvements in disease-free and overall survival among patients randomized to receive paclitaxel might be due to the longer duration of treatment for patients on the paclitaxel arm, the addition of a taxane that is noncross-resistant with cyclophosphamide and doxorubicin, or a combination of these two factors. Several studies that are each too small to draw independent conclusions provide support for the conclusion that the addition of taxane is an important element. In one of these trials, 524 patients were randomized to either four cycles of CAF (CA plus 5-fluorouracil) and four cycles of paclitaxel or eight cycles of CAF (Thomas, Buzdar, et al., 2000). About half of these patients received chemotherapy before surgery; 15 percent had T3 lesions, but 28 percent were node-negative. At 4 years there were 75 events. Disease-free survival was improved, and there was a 26 percent reduction in recurrences on the paclitaxel arm. However, these differences were not statistically significant.

The other study was designed for patients with large or locally advanced tumors, and all patients received primary chemotherapy with CVAP (cyclophosphamide 1000 mg/M^2, vincristine 1.5 mg/M^2, doxorubicin 50 mg/M^2, prednisolone 40 mg daily x5) at 3-week intervals

(Hutcheon, Ogston, Heys, et al., 2000). The 104 patients who had a complete or partial response after four cycles of CVAP were randomized to either another four cycles of CVAP or to four cycles of docetaxel (100 mg/M^2 at 3-week intervals) before undergoing surgery. After all eight cycles of chemotherapy had been administered, there was a highly significant improvement in both the clinical and pathological response rates for those on the docetaxel treatment arm.

Conclusions

The addition of four cycles of paclitaxel after the completion of a standard course of CA substantially improves disease-free and overall survival of patients with early breast cancer.

In light of more recent smaller but nonconfounded studies that demonstrated an advantage from adding four cycles of single agent taxane to four cycles of a doxorubicin-containing regimen, it is highly unlikely that all of the benefit for patients on the paclitaxel arm of this study is due simply to the longer duration of treatment in that arm of the trial.

The decision to use any form of adjuvant chemotherapy should be taken thoughtfully in a patient with a receptor-positive tumor scheduled to receive adjuvant tamoxifen. However, the evidence from this trial is not now sufficient to determine which chemotherapy regimen should be selected for these patients because this was an unplanned subset analysis, and the large trend towards a greater effect in receptor-negative patients was not statistically significant.

When patients receive breast radiotherapy in addition to chemotherapy, it is reasonable to wait until completion of 6 months of CA plus paclitaxel before starting the radiotherapy.

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Evaluating the Use of Paclitaxel Following Doxorubicin/Cyclophosphamide in Patients With Breast Cancer and Positive Axillary Nodes

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This study seeks to determine whether four cycles of paclitaxel (Taxol) given after four cycles of postoperative doxorubicin/cyclophosphamide (AC) prolongs survival and disease-free survival (DFS) relative to four cycles of AC alone, in patients with operable breast cancer and histologically positive axillary lymph nodes. Between August 1, 1995, and May 22, 1998, 3,060 patients were randomly assigned to receive either four cycles of AC (60/600 mg/M^2) every 21 days, or four cycles of AC followed by four cycles of Taxol given at 225 mg/M^2 as a 3-hour infusion every 21 days. Beginning on the first day of chemotherapy, all patients $\geq$50 years of age and those <50 years of age with tumors that were estrogen receptor (ER)-positive or progesterone receptor (PgR)-positive received tamoxifen 20 mg orally daily for 5 years. Patients treated with lumpectomy received radiotherapy following chemotherapy. Definitive analysis of the study was scheduled to take place following the report of the 490th death. On October 2, 2000, the third of five scheduled interim analyses was presented to NSABP's Independent Data Monitoring Committee (DMC), based on a median followup of 34 months, 269 total deaths, and 551 total events. The DMC subsequently recommended that these interim findings be considered for presentation to the Consensus Conference. As of the third interim analysis, no statistically significant difference between the two arms (control and treatment) either in terms of survival (133 deaths on the control arm, 136 on the treatment arm, relative risk=1.00, 95 percent CI=[0.78 to 1.27], p=0.98) or DFS (282 events on the control arm, 269 on the treatment arm, relative risk=0.93, 95 percent CI=[0.78 to 1.10], p=0.38). Estimated survival at 36 months is 92 percent for the AC arm and 90 percent for the AC$\rightarrow$Taxol arm; estimated DFS at 36 months is 81 percent in both arms.

Taxanes in the Adjuvant Setting: Why Not Yet?

Martine J. Piccart, M.D., Ph.D., Caroline Lohrisch, and Luc Duchateau

Adjuvant chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) and anthracycline-based regimens is associated with significant reductions in breast cancer mortality (EBCTCG, 1998). Numerous other treatment strategies have been explored in attempts to further improve survival, including newer anticancer drugs with demonstrated activity in the metastatic setting, such as the taxanes (T). So far, two randomized trials of the adjuvant taxane paclitaxel have been reported. An Intergroup trial (Henderson, Berry, Demetri, et al., 1998) compared the efficacy of 4 AC with 4 AC followed by 4 paclitaxel (AC→T) in node-positive cancer, while the M.D. Anderson Cancer Center trial compared 8 FAC to 4 T followed by 4 FAC (T→FAC) in node-negative and node-positive breast cancer (Thomas, Buzdar, Theriault, et al., 2000). The positive results in the Intergroup trial (overall survival [OS] 95 percent versus 97 percent, $p=0.04$, and disease-free survival [DFS] 86 percent versus 90 percent, $p=0.0008$) led to approval by the Food and Drug Administration (FDA) of adjuvant paclitaxel for node-positive breast cancer. The absolute survival difference, however, is quite small, just below the 5 percent significance level. The Anderson trial, reported subsequently, showed nonsignificant results (DFS 81.5 percent versus 85.2 percent, $p=0.2$, and 15 deaths versus 13 deaths for T→FAC and FAC, respectively).

The Intergroup and Anderson trials had important differences in design and patient eligibility. The proportion of patients in the Anderson trial with none, 1 to 3, or more than 3 positive nodes was approximately one-third each. This group therefore had a slightly better overall prognosis than the Intergroup population, in which no patients were node-negative and the proportion with 1 to 3 and more than 3 nodes was approximately even. More importantly, the two trials differed substantially with respect to total sample size and median followup. The Intergroup trial involved 3,170 patients, versus 524 in the Anderson trial, while the Anderson had more than double the median followup (18 months versus 43 months). In using a time-to-event analysis, the power of a trial to detect a significant effect rests primarily on the number of events. Thus, it is completely plausible that the Intergroup trial demonstrated a significant difference, given its approximately 374 events (DFS) and 125 deaths at 18 months, while the Anderson trial, with 75 events and 28 deaths, does not, despite longer followup. To what extent these differences influence the apparently disparate results of these two studies is not clear. Nevertheless, the conclusion must be that the results of the Anderson trial neither help nor hinder the case for adjuvant paclitaxel. There are, however, a number of reasons to support the view that the FDA may have made a hasty decision. Note that, after reviewing the same data, the European Regulatory Agency decided not to approve paclitaxel for adjuvant therapy.

Confidence in any treatment depends on whether its value is consistently reproducible. The general view within the scientific community is that a single randomized trial does not constitute sufficient level I evidence, no matter how compelling the results. This view arises from repeated observation that a particular regimen's superior results cannot always be duplicated in subsequent trials. Despite that well-known principle, the FDA seems to have been

persuaded by the results of only one trial. Given that numerous ongoing randomized trials of taxanes will be reported in the next few years and that the absolute survival difference reported by the Intergroup trial was modest (2 percent), it would have been more prudent to await corroborative evidence before approving the routine use of adjuvant taxanes.

Design Limitations of Intergroup Trial

Furthermore, the Intergroup trial had design limitations, and it is unclear to what extent those limitations accounted for the treatment effect. A major potential confounder in this trial was the duration of therapy, which was 12 weeks longer in the taxol-containing arm. Several trials have demonstrated that duration of therapy may indeed influence outcome, but reports on the trials do not deal with the relative importance of duration of therapy and cumulative dose. Both of these factors may have biased the results in favor of the AC→T arm, since the cumulative dose of doxorubicin in one-third of the study population was 240 mg/M^2, which may be suboptimal.

The Oxford overview reported that anthracycline therapy may be associated with a small survival advantage over CMF (EBCTCG, 1998), but other studies have failed to demonstrate that anthracycline therapy beyond a threshold dose improves survival. There does seem to be a dose-response relationship below that threshold, with compromised efficacy of anthracyclines (Wood, Budman, Korzun, et al., 1994; Bonneterre, Roche, Bremond, et al., 1998). Thus, we are faced with the question of whether the cumulative dose of doxorubicin in 4 AC (240 mg/M^2) was below this threshold, making it as effective as CMF but less effective than it could be. If the answer is yes, it may explain the apparent discrepancy in the results of NSABP B-15 (equivalence for 6 CMF and 4 AC 240 mg/M^2 doxorubicin total dose), the National Cancer Institute of Canada (NCIC) comparison of CEF and CMF (CEF giving a 7 percent superior OS, 720 mg/M^2 epirubicin total dose), and the Intergroup trial of CAF versus CMF (CAF giving a 2 percent superior OS) (Hutchins, Green, Ravdin, et al., 1998; Levine, Bramwell, Pritchard, et al., 1998). Although 4 AC (doxorubicin 60 mg/M^2/cycle) is a standard adjuvant regimen in North America, many European clinicians give several cycles of CMF following 4 AC, or a higher total dose of anthracyclines, such as can be found in CAF→FAC and CEF→FEC regimens.

Another major concern with the Intergroup trial is the immaturity of the data. The initial results were reported 8 months after the accrual of the last patient (3-year accrual period), based on a preplanned interim analysis of 450 events. These significant results cannot be extrapolated to later points in time unless one assumes a constant proportional hazards model. If that assumption is not correct, however, more mature results could show a "reversal of fortune," as did the EORTC neoadjuvant breast cancer study (Sylvester, Bartelink, Rubens, 1994). An interim analysis demonstrated significant superiority for chemotherapy, but reanalysis 2.5 years after the last patient was accrued reversed the favorable outcome of hormonal therapy, thus demonstrating the limitations of analyses based on early data. The Intergroup analysis, carried out when, on average, 96 percent of the patients were still alive and 88 percent were disease-free, is no exception. One could even call the more recent analysis (at 30 months median followup) immature, given the recurrence rate in the control arm of 22 percent, since a higher final recurrence rate for a node-positive population treated with anthracyclines would be expected,

based on previous trials (Fisher, Brown, Dimitrov, et al., 1990; Levine, Bramwell, Pritchard, et al., 1998).

Finally, there is the issue of whether all patients in the study derived equal benefit from the treatment. A subset analysis suggests that only patients with hormone receptor (HR)-negative tumors (one third of the study population) benefited from the addition of tamoxifen. For the 2,066 HR-positive patients, the hazard ratio for recurrence was 0.92 (95 percent CI 0.73-1.16) for AC→T versus AC, while for HR-negative patients it was 0.68 (95 percent CI 0.55-0.85).

A similar trend was observed in the Anderson trial: 58 percent of the population was HR-positive, and although not statistically significant, the absolute difference in DFS for FAC versus T→FAC was 3 percent for HR-positive patients and 5 percent for HR-negative patients.

There are several potential explanations for these findings. Either the baseline risk for HR-positive tumors is lower and therefore a benefit of tamoxifen is more difficult to demonstrate or does not exist, or the baseline risk is sufficiently lowered by AC and tamoxifen that the added benefit of tamoxifen, if it exists, cannot be demonstrated with this sample size and followup period. Another explanation may be that recurrences in the HR-positive population occur later, and a benefit may only become apparent with longer followup. Regardless of the reason, this subset analysis supports the contention that, based on the available evidence, sweeping generalizations about the value of adjuvant paclitaxel are premature.

Unsettled Issues

Despite the enormous strides made in adjuvant chemotherapy for breast cancer over the last 20 years, there are a number of unsettled issues. The NCIC trial faces the ambitious task of exploring the relative importance of cumulative dose, dose density, and noncross-resistant drugs added to anthracycline-based chemotherapy. The design calls for randomization between three arms: 6 FEC (Levine regimen), 4 AC followed by 4 T, and 6 EC every 2 weeks with G-CSF followed by 4 T. If the results were available now, we might be able to put to rest many of our reservations about the Intergroup trial, which leave us a little unsettled about the long-term reliability and generalizability of its results, regardless of how promising they may appear. Unfortunately, the results are not available, and the finding of nonsignificance in the Anderson study amplifies the uncertainty. It is necessary to wait for future results of ongoing trials before pronouncing judgment on the value of taxanes in the adjuvant setting.

It is also necessary to better define the population most likely to benefit from therapies of longer duration, intensification, and multiple regimens. It no longer is reasonable to judge all breast cancer patients as having equal probability of benefit from a given therapy. That was a paradigm that worked well when adjuvant chemotherapy for breast cancer was in its infancy and little was known about the molecular heterogeneity of breast cancer. It is now of critical importance to design trials with the aid of molecular tumor profiles with potential predictive value to prospectively identify the subgroup most likely to benefit from the addition to therapy of taxanes and other new drugs. This process has begun with the EORTC-Breast Cancer Cooperative Group trial in locally advanced breast cancer—an attempt to examine the predictive value of p53 mutations in response to taxane chemotherapy.

It is to be hoped that the early promise of taxanes in adjuvant treatment of breast cancer will be confirmed, since there are few encouraging alternatives at this time. It is important to realize, however, that the data we have now only support their potential. Further followup, and trials that corroborate the results of the Intergroup trial of AC versus AC→T, are essential to define the value of taxanes in early breast cancer.

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Preoperative Chemotherapy: NSABP Protocols B-18 and B-27

Norman Wolmark, M.D.

If the sole purpose of this review were to determine whether preoperative chemotherapy should be used as part of the standard armamentarium in the treatment of breast cancer, the answer would be straightforward if not banal. Since the data have clearly demonstrated that there is no disadvantage to the use of preoperative chemotherapy with respect to disease-free survival and survival, its use as an intervention to downstage tumors, making them amenable to breast-preserving procedures, is not likely to generate intense controversy. To view preoperative chemotherapy in this narrow context, however, belies its compelling biologic significance.

The emergence of preoperative adjuvant therapy as an intervention in primary operable Stage I and II breast cancer is a direct consequence of data generated from a series of randomized prospective clinical trials. The rationale and justification for this intervention evolved on the heels of the retreat from radical mastectomy. Only with the acceptance of breast-preserving operations and the abandonment of en bloc resection could the primacy of the operation be challenged. The tentative and seemingly heretical question could finally be addressed: Should the operation now be regarded as adjuvant treatment? In order for this hypothesis to reach the point where it could be tested in randomized prospective clinical trials, it first had to be demonstrated that adjuvant therapy when used in the traditional postoperative setting could prolong disease-free survival and survival in both stage I and II carcinoma of the breast.

NSABP B-18 was conceptually provocative in that preoperative chemotherapy was given to women with tumors that were readily amenable to treatment by more traditional means. These were not women with locally advanced breast cancer whose tumor had reached the point where it was no longer “curable” with operative intervention and in whom chemotherapy was used as “salvage” treatment. But perhaps the greatest potential of preoperative adjuvant therapy is yet to be realized. This is a unique setting—the tumor is readily accessible to surgery while the patient is undergoing other treatment. A potentially powerful tool may become available whereby molecularly characterized tumor discriminants can be correlated with the efficacy of preoperative adjuvant treatment and, more importantly, with subsequent survival. Although it is premature to suggest that objective tumor regression during the course of adjuvant therapy is a definitive bioassay that presages efficacy, the data for NSABP B-18 suggest that this is a possibility.

NSABP Protocol B-18

Between October 1988 and April 1993, 1,495 eligible patients were randomized to receive either four cycles of Adriamycin (A) and cyclophosphamide (C) preoperatively followed by surgery, or to the same chemotherapeutic regimen administered in the traditional

postoperative setting. Eligibility was restricted to women with clinical Stage I and II breast cancers whose tumors were palpable. Because minimal perturbation of the tumor in the preoperative setting was thought to be essential, open biopsy was not permitted; the diagnosis was established by either fine needle aspiration or core needle biopsy. In those women undergoing breast-preserving procedures, radiotherapy was administered within 4 weeks of the operation in the preoperative arm and within 4 weeks of the completion of chemotherapy in the postoperative arm. Over a quarter of the women in this trial had tumors whose diameter was > 2 cm in diameter.

The data at six-year followup demonstrate definitively that the four cycles of preoperative chemotherapy used in this trial were effective in downstaging the size of the primary tumor and of involved regional nodes. Of the 685 women undergoing preoperative chemotherapy, 36 percent demonstrated a complete clinical response with no evidence of palpable residual tumor at the completion of chemotherapy. An additional 43 percent demonstrated a partial response to treatment, providing an overall objective response of 79 percent. Of the 36 percent of women demonstrating a complete clinical response, approximately one-third had no evidence of invasive cancer by histologic exam of the operative specimen. There also was evidence of nodal downstaging attributable to preoperative chemotherapy; 58 percent of women randomized to traditional postoperative chemotherapy had histologically positive nodes, compared with 40 percent of those patients who received preoperative chemotherapy.

The overall rate of ipsilateral breast tumor recurrence (IBTR) in those women undergoing breast-preserving operations was 7.9 percent for those who received preoperative chemotherapy, compared to 5.8 percent in those who were treated with postoperative therapy. Since there were only 66 ipsilateral breast tumor recurrences in the 954 eligible patients with breast-preserving procedures, further subset analysis of IBTR relative to patient age, tumor size, and initial response to therapy is of questionable merit.

The data are equally noteworthy for what was not demonstrated. There was no advantage for preoperative chemotherapy relative to disease-free survival and overall survival. The life table curves for the two treatments were virtually superimposable. These findings are significant when related to the specific aims of the trial. Prior to the initiation of NSABP B-18, it was postulated—on the basis of a number of kinetic models—that preoperative chemotherapy would be superior to chemotherapy given in the postoperative setting. One popular kinetic model suggested that as a result of spontaneous mutations a progressively increasing subset of drug-resistant cells developed with time, thus favoring the preoperative setting. The results of NSABP B-18 are not supportive of this hypothesis.

Perhaps the most interesting finding of NSABP B-18 is the correlation between local tumor response and subsequent outcome. Women who demonstrated a complete clinical tumor response had a better outcome than those who did not. Moreover, the most favorable outcome occurred in women who had no evidence of residual histologic invasive cancer. In a multivariate analysis in which other baseline prognostic variables were included, breast tumor response to preoperative chemotherapy continued to be a significant independent predictor of patient outcome (Fisher, Brown, Mamounas, et al., 1997; Fisher, Bryant, Wolmark, et al., 1998).

NSABP Protocol B-27

This later study was a natural extension of B-18. Patients with similar characteristics to those in B-18 are randomized to one of three treatment options, all utilizing preoperative chemotherapy. The control arm consists of the same regimen that was used in the preoperative setting of B-18, namely, four cycles of AC. Arm 2 will determine whether adding four additional preoperative cycles of sequential Taxotere following AC will result in a higher proportion of women with clinical and pathologic tumor response. Patients randomized to the third arm receive the same preoperative four cycles of AC, with the four cycles of Taxotere delayed until after the operation has been completed. The trial was initiated in December of 1995, and the required sample size of 2,400 patients is expected to be achieved by the end of this year.

B-27 will assess whether the addition of the taxane regimen will prolong disease-free survival and survival, and whether these endpoints can be correlated with the response of the primary tumor. The preoperative setting provides the opportunity to evaluate serial changes in serum and tumor biomarkers, and to correlate such changes to tumor response and patient outcome. As part of this study, formalin-fixed and paraffin-embedded core biopsy or fine needle aspiration have been collected for biomarker studies. It will be possible, using the collected materials, to evaluate the prognostic and predictive value of several biomarkers, including HER2, p53, p-glycoprotein, Ki67, and array-based CGH (Mamounas, 1997).

Conclusions

If the correlation between tumor response and outcome observed in B-18 can be verified and extended in B-27, a rapid evaluation of candidates for therapeutic intervention could become available. Although it is tempting to speculate on the potential biologic contributions of the preoperative setting, the practical charge of the consensus committee must be addressed: Should preoperative chemotherapy be part of the therapeutic standard? The data support the use of adjuvant preoperative chemotherapy in settings where the downstaging of the primary tumor is desirable, and in this context it should be an accepted standard of care. Updated results of B-18 and results from other preoperative chemotherapy trials will be reviewed during this conference. Although the information generated so far is unlikely to represent a threat to the domain of the surgeon, the primacy of the operative procedure has been significantly challenged.

Table 1. Clinical response to preoperative chemotherapy

	N	%
Complete	249	36
Partial	296	43
Stable	118	17
Progressive	22	3

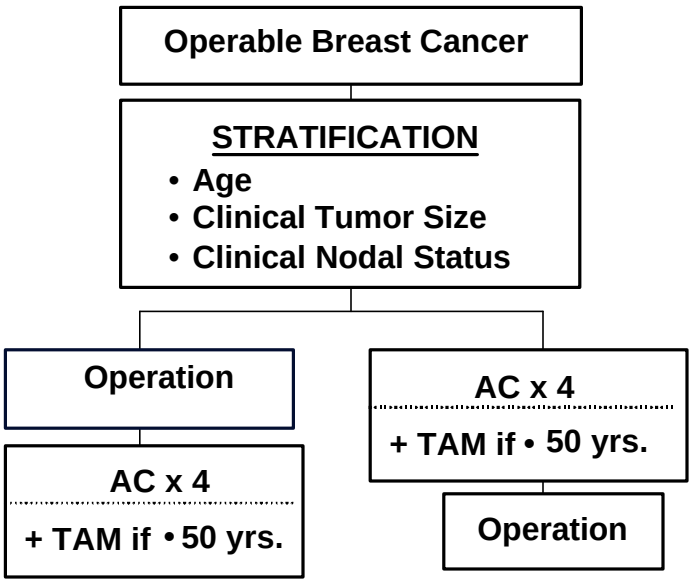

Figure 1. NSABP Protocol B-18

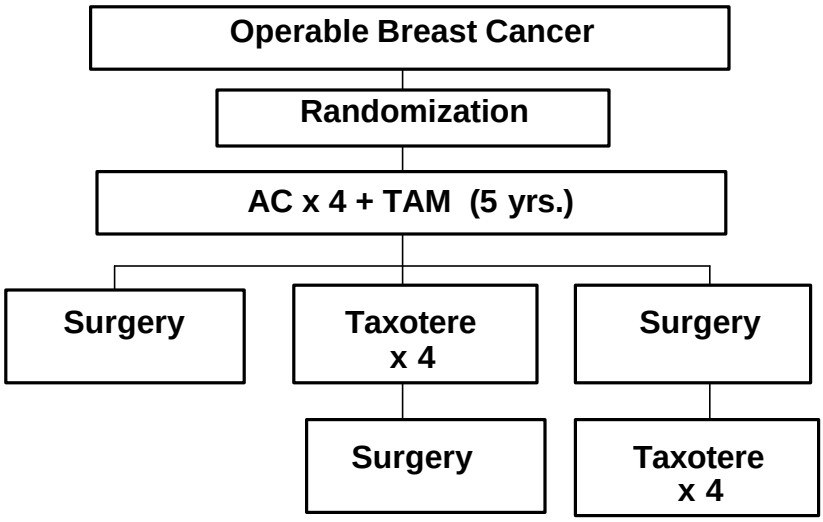

Figure 2. NSABP Protocol B-27

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Who Should Not Receive Chemotherapy?—International Databases

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Adjuvant use of chemotherapy and tamoxifen probably saves more lives than any other medical therapy for cancer (Bergh, 2000; EBCTCG, 1998a; EBCTCG 1998b). Despite this major achievement, the principal problem in adjuvant therapy is selecting patient subgroups to receive any particular therapy. Data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrate that a relatively large proportion of treated patients will relapse despite CMF or anthracycline-based adjuvant therapy with or without tamoxifen. In the future we hope to have a detailed bio-molecular "fingerprint" of each cancer that will allow us to tailor an optimal approach for each patient, combined with an appreciation of pharmacokinetic variation. Recent data using microarray technology strongly indicate that "fingerprints" have a very high degree of complexity (Perou, Sörlie, Eisen, et al., 2000).

The most critical issue today is to find the optimal balance between patients who should be offered adjuvant therapy and those who are at a sufficiently low risk not to be offered such therapy. In addition, those selected should be given a specific and targeted therapy that avoids the problem of relapse. Cut-off levels and recommendations for adjuvant therapy vary from country to country and region to region, most likely reflecting medical, economic, or cultural differences.

Our goal is to identify women who are at sufficiently low risk of relapse that they need not be offered adjuvant chemotherapy. We will review data from population-based cancer registries in the Nordic countries, together with country-based and regional registries containing information on adjuvant therapy modalities, as well as information from the Swedish mammography program. This will be possible because the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) have had population-based cancer registries for several decades. The broad coverage of these registries provides extensive data on the incidence of cancer and on mortality from the various kinds of cancer. Information on prognostic factors and on therapy, however, are not included in these national registries, except for those of Denmark and Sweden.

Beginning in 1977, the Danish Breast Cancer Group (DBCG) began to develop a population-based cancer registry (Mouridsen, personal communication). The registry contains the names of around 60,000 Danish women who have had breast cancer. The present annual incidence of breast cancer in Denmark is around 3,500. A retrospective analysis of 30,000 women with breast cancer made it possible to identify a group with a low risk of relapse (Mouridsen, personal communication). This group consists of approximately 20 percent of the patients in the registry. "Low-risk" is defined as a receptor-positive node-negative grade I (Bloom-Richardson) primary cancer less than 20 mm. The patients in this low-risk group were treated with mastectomy or breast-conserving surgery. Local radiotherapy was administered to the breast parenchyma remaining after breast-conserving surgery or to the scar area at the deep resection border in the case of nonradical surgery (Mouridsen, personal communication).

Using age-matched controls, it was found that the 5-year survival rate for all premenopausal Danish women (the control group) was 98 percent; the premenopausal low-risk group with breast cancer had the same 5-year survival rate of 98 percent (Mouridsen, personal communication). The corresponding figure for the entire postmenopausal group was 92 percent, and for the breast cancer cohort 91 percent (Mouridsen, personal communication). The team at DBCG is presently analyzing the 10-year figures.

The Stockholm (Sweden) Breast Cancer Group was established in 1976 and has a database containing the names of around 20,000 breast cancer patients (Rutqvist, personal communication). The annual incidence of new breast cancers in the Stockholm-Gotland region is from 1,200 to 1,300, from a population base of between 1.7 to 1.8 million. The registry covers between 85 and 90 percent of the women with breast cancer within that geographic region.

There is also an Uppsala-Örebro breast cancer registry in Sweden that started operation on September 1, 1992. That registry listed 10,610 patients as of August 25, 2000 (Degerman, personal communication). The population base is around 1.9 million.

We will use these registries to identify low-risk groups with a sufficiently good prognosis that makes it unlikely that these women would benefit from adjuvant therapy, as suggested by DBCG data or using other criteria, with the assistance of Lars-Erik Rutqvist of Stockholm and Lars Holmberg of Uppsala, Sweden, and their collaborators. With the assistance of Lazlo Tabar of Falun, Sweden, we will also use mammography-based data to identify low-risk groups.

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Who Should Not Receive Chemotherapy?—U.S. Databases and Trials

Monica Morrow, M.D.

Breast cancer patients in whom chemotherapy could be avoided include (1) those with an extremely favorable prognosis who are unlikely to experience any meaningful prolongation of survival from a treatment that is potentially both toxic and costly, (2) those in whom clear evidence of benefit from chemotherapy is lacking, and (3) patients in whom the toxicity of chemotherapy outweighs the benefits.

Favorable Prognosis Groups

Subsets of node-negative breast cancer patients with a favorable prognosis have usually been defined on the basis of tumor size or histologic subtype. Several large studies indicate that patients with tumors less than or equal to 1 cm in size have survival rates in excess of 90 percent. In the Breast Cancer Detection Demonstration Project (BCDDP), stage I cancers had an 8-year survival of 90 percent, and for those less than 1 cm in size, survival was 95 percent (Seidman, Gelb, Silverberg, et al., 1987). These figures are similar to data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute from the same time period, where 8-year survival for stage I carcinoma (n=5,479) was 92 percent (Carter, Allen, Henson, 1989). In the BCDDP group of tumors less than 1 cm in size, survival was 96 percent for screen-detected tumors and 94 percent for interval cancers. In both BCDDP and SEER, survival rates greater than 90 percent were reported for women both under and over age 50. In a subsequent SEER report, 5-year survival was 99.2 percent for 269 tumors less than 0.5 cm and 98.3 percent for the 791 tumors between 0.5 and 0.9 cm in size (Henson, Ries, Freedman, et al., 1991). In NSABP B-21, a study of invasive carcinomas less than or equal to 1 cm with negative axillary nodes, 5-year survival was 97 percent for the 1,009 patients under study, regardless of treatment (radiotherapy, radiotherapy plus tamoxifen, tamoxifen). A subset of patients with node-negative tumors less than 1 cm with a poor prognosis has not been identified. The National Cancer Data Base (NCDB) reported a 5-year survival of 98.4 percent for 22,288 patients with tumors less than 1 cm diagnosed between 1985 and 1991. For the subset of patients with tumor grade, survival ranged from 98.6 percent for grade 1 tumors to 96.0 percent for grade 3 tumors.

The addition of histologic grade and histologic tumor type to size allows expansion of the pool of favorable patients who will receive minimal benefit from chemotherapy. A SEER report combining stage and grade found a 95 percent 5-year survival for grade 1, stage I patients versus 83 percent for grade 3, stage I patients. Rosen, Groshen, Kinne, et al. (1993) observed that 20-year disease-free survival for patients with breast cancer of special histologic types (tubular, mucinous, papillary, medullary, adenocystic) up to 3 cm in diameter was 87 percent. Although the favorable prognosis for medullary carcinoma is not confirmed in all reports, a literature review of 300 node-negative tubular cancers of all sizes (the majority with long-term followup)

identified only four relapses (1.3 percent). Failure to recognize the prognostic value of grade and histologic type assumes particular importance as the use of screening mammography continues to increase. There is a clear relationship between small tumor size and low histologic grade, and favorable subtypes such as tubular carcinoma are identified more frequently in screened populations, putting an increasing number of women with breast cancer at risk for overtreatment.

Lack of Clear Evidence of Benefit/Toxicity

The NSABP B-20 trial compared the use of tamoxifen alone to tamoxifen plus chemotherapy in estrogen receptor (ER)-positive breast cancer (Fisher, Dignam, Wolmark, et al., 1997). After 5 years, a 4 percent to 5 percent improvement in disease-free survival was seen with the addition of chemotherapy, and subset analysis failed to identify a subset of patients who did not benefit from the addition of chemotherapy. However, a detailed analysis of prognosis for the 4,000 node-negative, ER-positive patients who participated in NSABP B-14 found marked heterogeneity in the ER-positive patient population (Bryant, Fisher, Gunduz, et al., 1998). For the most favorable subset of patients (1 cm tumor, ER-positive, low S-phase), 10-year disease-free survival was 85 percent. For this group of patients, the addition of chemotherapy with a 30 percent reduction in events would result in an absolute disease-free survival benefit of only 3 percent to 4 percent at 5 years. For patients age 60 to 70, an increased hazard of death was noted compared to those in their 50s. However, after correction for second primary cancers and deaths due to other causes, the rate of treatment failure was constant for women over age 50. In the age 60 to 70 group, the absolute benefit of chemotherapy should be assessed in the context of the patient's overall health status and risk of death from other causes.

For patients age 70 and older with ER-negative cancers, evidence of a survival benefit from adjuvant chemotherapy is less clear. The Oxford overview showed no improvement in relapse-free or overall survival after chemotherapy in this group, but only 600 women over age 70 were available for analysis. Diab, Elledge, Clark (1999) examined the outcome of 401 patients age 75 and older who received no adjuvant therapy. Five-year overall survival for the node-negative patients was 70 percent, compared to 69 percent for the general population matched for age and sex. Desch and colleagues used a Markov model to estimate the benefit of chemotherapy in ER-negative patients with stage I breast cancer (Desch, Hillner, Smith, et al., 1993). The gain in life expectancy for a 75-year-old was 2.9 months, which fell to 1.8 months after adjustment for quality of life. For the entire group of women age 60 to 80, the average survival benefit never exceeded the duration of chemotherapy.

Based on the preceding information, chemotherapy does not appear to be warranted in (1) any subset of women with node-negative breast cancers less than 1 cm in size; (2) women with node-negative, special histologic subtypes of cancer up to 3 cm in size; (3) grade 1, stage I breast cancers; (4) ER-positive, node-negative patients in favorable prognostic groups; and (5) node-negative, ER-negative patients over age 70.

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A Prospective, Randomized Comparison of Two Doses of Combination Alkyating Agents (AA) as Consolidation After CAF in High-Risk Primary Breast Cancer Involving Ten or More Axillary Lymph Nodes (LN): Preliminary Results of CALGB 9082/SWOG 9114/NCIC MA-13.

William P. Peters, M.D., Ph.D., G.L. Rosner, D. Hurd, L. Norton, R. Schilsky

Despite conventional dose chemotherapy, the prognosis remains poor for primary breast cancer patients with multiple involved axillary lymph nodes. Between January 1991 and May 1998, we treated 874 women with Stage II or IIIA breast cancer involving ten or more axillary lymph nodes in a prospective, randomized study evaluating intensive alkyating agents (AA) consolidation after CAF. The median age of the patients was 45 (range 22 to 66), the median tumor size was 3.05 cm, and the median number of involved lymph nodes was 14 (range 10 to 52). Nineteen percent of the patients had more than 20 involved lymph nodes, and 69 percent were hormone receptor (HR)-positive.

Eligible patients were treated with four cycles of CAF (600/60/1200 mg/M^2 q 28 days). Ninety-nine of the patients who were entered were not randomized, including 24 for recurrent breast cancer, 2 who died of CAF toxicity, 26 denied insurance coverage, 17 who withdrew, 13 who were ineligible, and 7 others. Of those remaining, 394 were randomized to high-dose CPB (HDCPB: cyclophosphamide [5625 mg/M^2], cisplatin [165 mg/M^2], and BCNU [600 mg/M^2], with BM and PBPC support), and 391 to intermediate dose CPB (IDCPB: C: 900 mg/M^2, P: 90 mg/M^2, and B: 90 mg/M^2), with G/CSF support. Patients relapsing on intermediate dose CPB were eligible for subsequent ABMT. All patients were planned for local-regional radiotherapy, and HR-positive patients received tamoxifen for 5 years.

An early outcome analysis was performed in 1998 with only 60 percent of the expected number of events, which appeared at the median followup of 37 months. The intent-to-treat EFS and OS comparisons between high dose and intermediate dose CPB were inconclusive (68 percent versus 64 percent, p=0.7; 78 percent versus 80 percent, p=0.1, log rank test).

Therapy-related events were concentrated in the first year, and there was a reduction in relapses and a trend in age-related toxicity. We will provide updated followup on this study. Although additional studies are required to resolve the role of high-dose consolidation therapy in this setting, the information reported here may be of value to women evaluating treatment options.

Overview of the Six Randomized Adjuvant Trials of High-Dose Chemotherapy in Breast Cancer

Karen H. Antman, M.D.

There are six reports of randomized trials of high-dose chemotherapy in high-risk primary and metastatic breast cancer (see table 1). However, the South African study has been discredited, and two of the remaining studies randomized fewer than 100 patients and thus could not exclude a survival difference of 30 percent. The Scandinavian study did not compare high-dose versus conventional dose therapy. Thus, there have been two reasonably large trials, but both with only about 3 years of median followup at the time of the last analysis.

Table 1. Reports of randomized trials of high-dose therapy in high-risk primary and metastatic breast cancer.

	Number Randomized	% Toxic Deaths		Med Yrs FU	% 3 year EFS		*p* value	% 3 year S		*p* value	Reference
		HDC	Control		HDC	Control		HDC	Control		
Dutch phase 3	885	0.9	0.2	3.5	72	65	.057	NA	NA	.31	Rodenhuis, 2000; McNamee
First 284 patient subset	284	NA	NA	7.0	77	62	.009	89	79	.039	Rodenhuis, 2000; McNamee
CALGB/ Intergroup	783	7.4	0	3.6	71	64	NS	79	79	.29	Peters
Scandinavian	525	0.7	0	2.0	68	62	NS	79	76	NS	Bergh
S African	Study discredited										Bezwoda, Weiss
Dutch phase 3 pilot	81	0	0	4.1	70	65	.97	82	75	.84	Rodenhuis 1998
M.D. Anderson Cancer Center	78	2.5	0	6.5	48	62	NS	58	77	NS	Hortobagyi

Code: HDC = high-dose chemotherapy; Med Yrs FU = median years followup; EFS = event-free survival; S = survival; NA = not available; NS = not significant.

Mortality was consistently low, in the 0 to 2.5 percent range, for the high-dose regimens except for the CALGB/Intergroup study, which had a 7.4 percent toxic mortality rate. Mortality for the more conventional dose arms was in the range of zero to 1 percent.

The Dutch trial was the largest of the six studies (885 patients randomized) and therefore had the greatest statistical power to detect modest differences (Rodenhuis, Bontenbal, Beex, et al., 2000; McNamee, 2000). It compared four courses of FEC (5-fluorouracil, epirubicin, cyclophosphamide) to either an additional cycle of FEC or to CTCb (cyclophosphamide, thiotepa, carboplatin) with stem cell support followed by surgery, radiation, and tamoxifen for 2 years. In a planned analysis of the first 284 patients, at a median followup of 6 years, disease-free and overall survival were significantly better for the group receiving high-dose therapy. In the study as a whole, the mortality was 1 of 443 patients on standard dose FEC and 4 of 442 on high dose CTCb. At a median of 3 years followup, a trend (p=.057) emerged favoring high-dose therapy.

The CALGB/Intergroup study compared high versus intermediate dose cyclophosphamide, BCNU, and cisplatin (CBP) after a CAF (cyclophosphamide, Adriamycin, 5 fluorouracil) induction (Peters, Rosner, Vredenburgh, et al., 1999). Although the study can be criticized on grounds that intermediate dose CBP is not a standard regimen, this design in scientific terms is a pure comparison between high and intermediate dose CBP.

This first generation BCNU-containing regimen (as noted earlier) had a 7.4 percent mortality rate, which varied with the experience of the transplant center and increased with patient age. Substantial pulmonary and hepatic toxicity also occurred. With a median of 3.6 years of followup at the time of presentation, the differences in the PFS and OS rates in the two groups were not significant. Fewer events occurred than would have been predicted from historical series, suggesting either patient selection or an effect of the intermediate dose CBP. Significantly, fewer relapses occurred in the high-dose arm, but the survival rate of the two arms was similar at 70 percent because of the early toxic mortality of 7.4 percent. Increased mortality neutralized this early benefit. The study group was selected to have a tumor mortality of ~80 percent. Survival in both arms will fall with time, and significant differences may or may not emerge.

The Scandinavian trial compared induction FEC followed by one high-dose cycle of CTCb versus six additional cycles of moderately high dose FEC. The doses (in mg/M^2) of FEC were tailored to individual tolerance up to 600 of 5-FU, 120 of epirubicin, and 1,800 of cyclophosphamide per cycle. The planned cumulative doses for tailored therapy actually exceeded that for the BMT arm. Therefore, this study assessed the role of high-dose therapy as compared to intermediate-dose chemotherapy with a higher cumulative dose (Bergh, 1999). Three percent of the patients on the tailored dose arm developed leukemia or myelodysplasia, compared with none on the marrow transplant arm.

Ongoing or unpublished randomized studies of high-dose therapy for breast cancer are shown in table 2.

Table 2. Adjuvant trials by number of involved axillary lymph nodes (LN+)

Eligible #LNs+	Chair	Group	Accrual Target	Accrual
>3	Leanard	UK, Anglo-Celtic	604	closed
>3	Gianni	Milan Cancer Institute	350	closed
>4	Russel/Nabholtz	Intl BCIRG	460	@ ~290
>4	Bearman	Intergroup	1,000	@ ~437
>7	Roche	Pegase 01	314	closed
>9	Zander/Seeber	2 German studies		
>9	Basser	Australia, IBCSG	340	closed
>9	Tallman	ECOG	550	closed

Additional followup of the two large randomized trials and the completion of ongoing randomized trials will provide more reliable data to determine the role of high-dose chemotherapy regimens in the management of high-risk primary breast cancer.

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Overview: Postmastectomy Radiotherapy

Jack Cuzick, Ph.D.

The first issue in cancer treatment to be addressed by a randomized trial was the role of radiotherapy in breast cancer. Although that trial took place in 1948, the question of whether radiotherapy is an appropriate treatment for breast cancer remains controversial. There is little doubt that radiotherapy is effective in improving local control of the disease. The rate of local recurrence with radiotherapy is reduced to about one-third of the rate when surgery alone is used, although this absolute reduction is very much dependent on the extent of the surgery and the nodal status of the patient (see table 1). The relative reduction in local recurrence is substantial in all trials and appears to be unaffected by patient age, nodal status, dose, axillary or internal mammary chain irradiation, adjuvant chemotherapy or tamoxifen, or time of trial commencement. Slightly better results are seen in larger trials and also in trials employing smaller doses of radiotherapy per fraction.

What is less clear is the effect of radiotherapy on patient survival. This question has been examined in five large studies since 1987. In the first, Cuzick and colleagues observed an increase in late mortality (Cuzick, Stewart, Peto, et al., 1987). A subsequent study (Cuzick, Stewart, Rutqvist, et al., 1994) found that this increase was due to cardiovascular mortality, but it also suggested that there might be a late reduction in breast cancer deaths. Two subsequent and much larger overviews have confirmed and extended these observations (EBCTCG, 1995; EBCTCG, 2000). The most recent study of radiotherapy involved the examination of the deaths of more than 10,000 women out of a total of about 20,000 women in 40 randomized trials worldwide. No clear effect of radiotherapy on total mortality was found, but the study found highly significant differences in breast cancer deaths and non-breast-cancer deaths (see figures 1 and 2). After 20 years of followup, breast cancer deaths were reduced by 4.8 percent, but non-breast-cancer deaths were elevated by 4.3 percent. Both of these changes were highly significant ($p< 0.001$). The change in non-breast-cancer deaths emerged later than the change in breast cancer deaths, the differences being 1.0 percent for breast cancer mortality and 3.0 percent for non-breast-cancer mortality at 10 years. Most of the excess non-breast-cancer deaths were due to vascular disease, which increased by 30 percent. There were no significant subgroup effects on the relative death rates from breast cancer and from non-breast-cancer causes. However, an increased absolute death rate was seen in the radiotherapy arm for older and for node-negative women, due to the lower ratio of breast cancer deaths to other kinds of death in those two groups. More recent trials have reported larger overall mortality benefits from radiotherapy, but the followup from these trials is shorter, so uncertainty remains about the long-term mortality effects, especially for non-breast-cancer deaths.

Table 1. Effects of radiotherapy allocation on 10-year probability of local recurrence, by type of surgery and nodal status*

	Isolated local recurrence (%)		
	Radiotherapy	Control	Absolute difference (SE)
Mastectomy alone			
Node-negative	11.3	28.6	17.3 (1.5)
Node-positive	15.5	44.9	29.4 (4.0)
Mastectomy with axillary sampling			
Node-negative	7.2	23.1	15.9 (2.8)
Node-positive	6.3	37.7	31.4 (1.9)
Mastectomy with axillary clearance			
Node-negative	2.7	9.2	6.5 (1.3)
Node-positive	9.0	24.4	15.4 (1.4)
Breast conservation with axillary clearance			
Node-negative	7.8	25.0	17.3 (1.7)
Node-positive	16.1	35.4	19.4 (3.4)
Subtotals			
All node-negative	7.9	23.2	15.3 (0.9)
All node-positive	9.3	32.0	22.7 (1.0)
Total	8.8	27.2	18.5 (0.7)

* 37 trials with data on local recurrence. All logrank tests for local recurrence yield $2p<0.00001$.

From EBCTCG (2000)

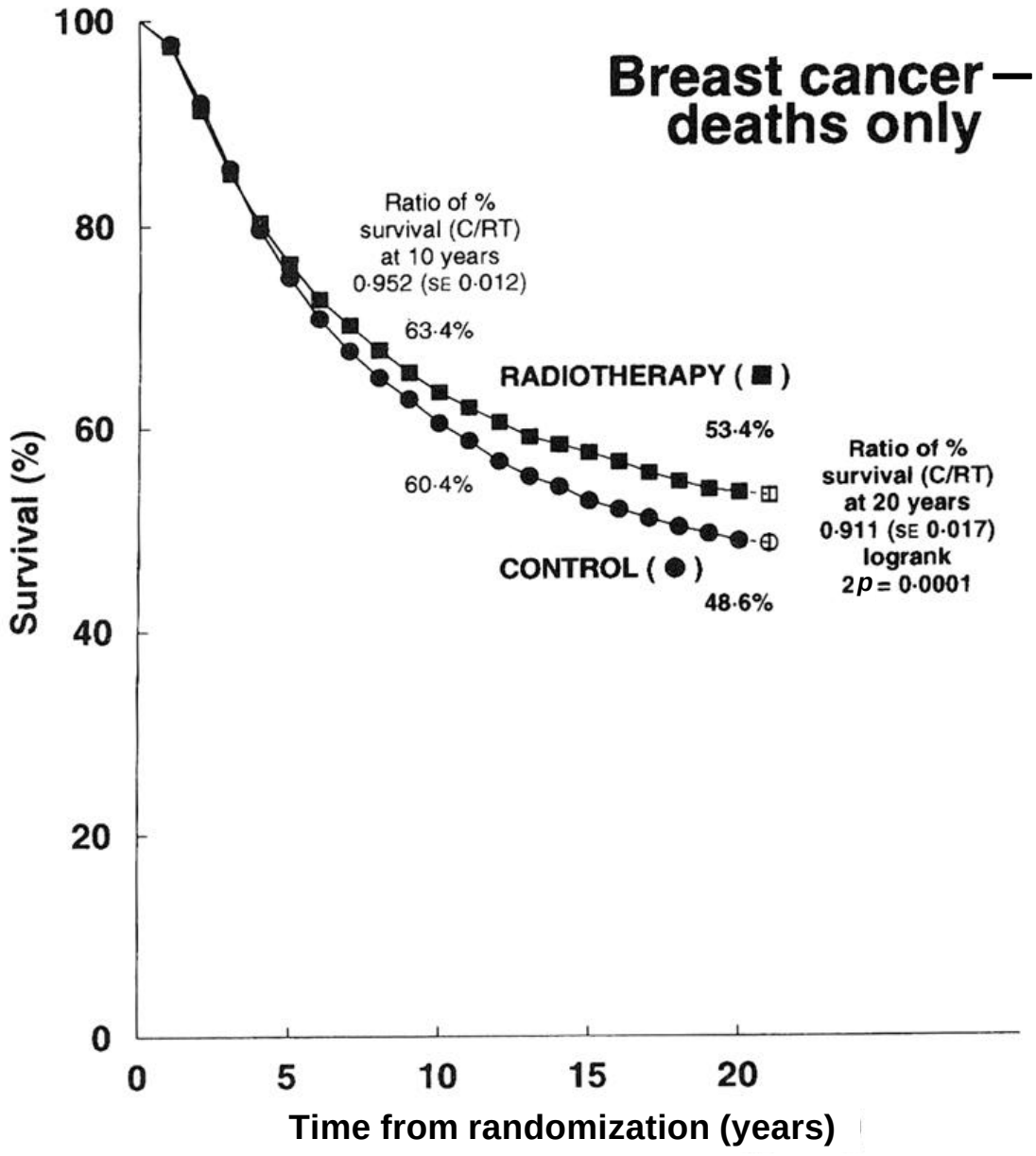

Figure 1. Radiotherapy and breast cancer deaths.

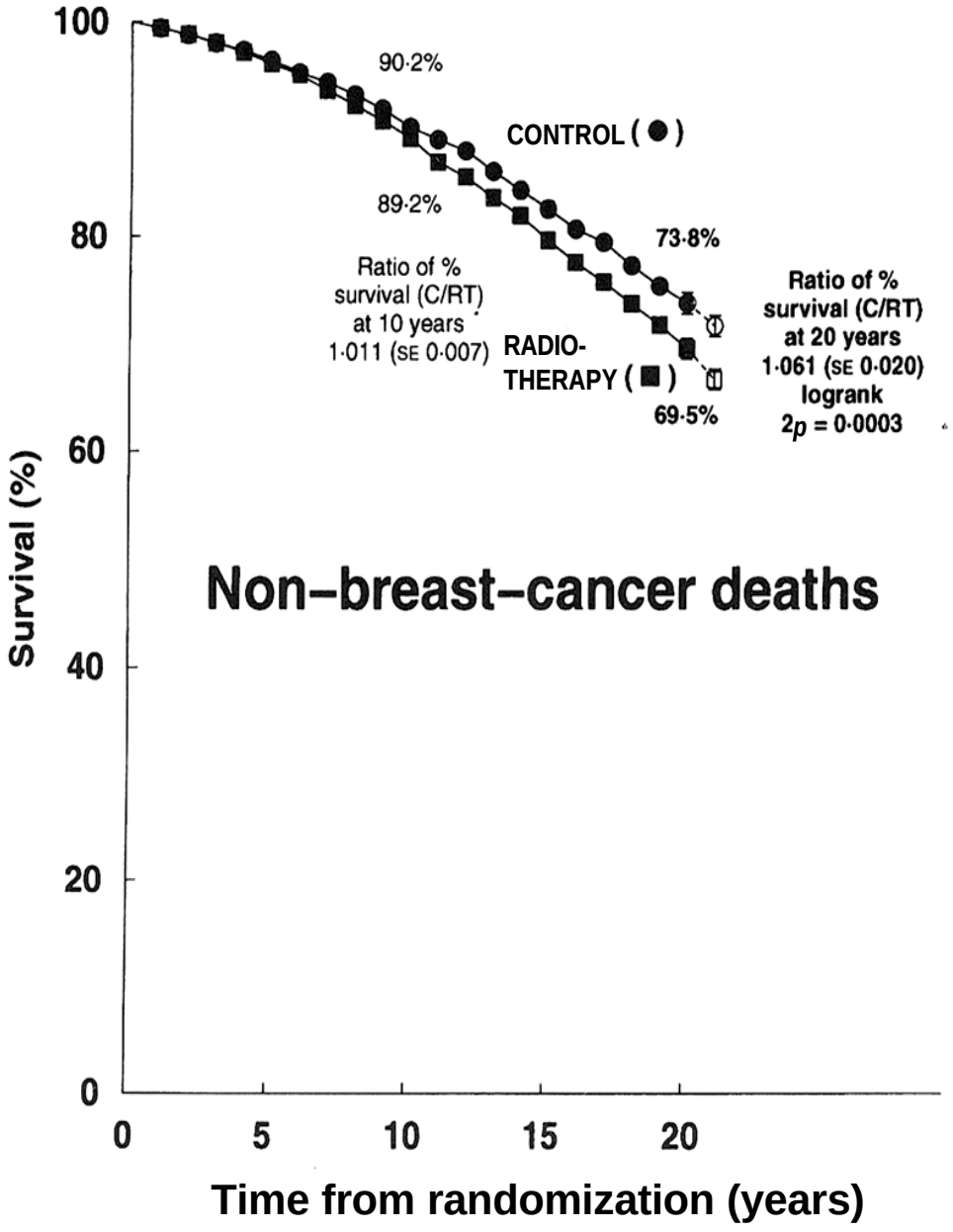

Figure 2. Radiotherapy and non-breast-cancer deaths.

Chief among these uncertainties is whether the newer kinds of radiotherapy, which allow for more accurate delivery of the dose, can achieve reduction in breast cancer mortality without increasing cardiovascular mortality. It will also be important to try to separate out the effects of radiation of the breast/chest wall versus radiation of lymph nodes. These questions are particularly relevant for women with small tumors or ductal carcinoma in situ (DCIS) who receive lumpectomy and radiotherapy, since their survival rate is very good and deleterious late effects would be most damaging.

It is clear that radiotherapy is of net benefit to patients who are at high risk of local recurrence and is inappropriate for others where the risk is low. Much uncertainty still exists about where to draw the dividing line between these groups and the extent to which improved techniques have shifted this boundary.

Preliminary data from the next overview (to be published in September 2000) will be available before the consensus development conference and should cast additional light on these uncertainties.

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Adjuvant Postmastectomy Radiotherapy: Review of Treatment Guidelines and Techniques

Lori Pierce, M.D.

Essentially every randomized trial conducted to date to examine the effects of radiotherapy following surgery in early-stage breast cancer has demonstrated a benefit of locoregional control by the addition of radiotherapy. This was evident in the recent update of the meta-analysis of postoperative radiotherapy for early-stage disease, where a two-thirds reduction in local recurrence was seen following radiotherapy (EBCTCG, 2000).

There is controversy, however, on whether this benefit can significantly impact the risk of systemic recurrence and improve overall survival. The meta-analysis demonstrated a significant reduction in breast cancer mortality in patients receiving radiotherapy, with a 13.2 percent proportional reduction in breast cancer-related deaths following radiotherapy. This reduction was counterbalanced, however, by a 21.2 percent proportional increase in non-breast-cancer deaths, primarily vascular, in women who received radiotherapy. It has been well-documented that the cardiac toxicity seen in the meta-analysis is primarily attributable to radiotherapy equipment and techniques used in earlier trials that are obsolete by today's standards. These results, however, underscore the importance of careful planning of treatment in the delivery of radiotherapy in maximizing a breast cancer patient's overall survival.

Examination of patients following mastectomy and chemotherapy in node-positive breast cancer has shown rates of isolated locoregional failure ranging from 13 percent to 40 percent, accounting for a third to a half of all relapses (Recht, 1999). Factors that undoubtedly contribute to this broad range include various tumor characteristics, such as extent of axillary node involvement, tumor size, presence of lymphatic invasion, estrogen receptor (ER) status, and tumor grade, as well as clinical factors, such as length of followup and (possibly) choice of systemic therapy. In some trials, chemotherapy has been shown to reduce the risk of locoregional recurrence by 40 to 50 percent; in other studies, however, there has been no perceivable effect. Locoregional recurrences also occur despite myeloablative doses of chemotherapy used in transplant studies. Thus, the inconsistent results seen with chemotherapy support the need for radiotherapy to achieve maximal locoregional control.

The locoregional sites at risk following mastectomy include the chest wall, supra- and infraclavicular nodes, internal mammary nodes, and axilla. The patterns of failure reported in most node-positive series show the chest wall and the clavicular regions to be the most common sites of failure following mastectomy, and they are the sites where locoregional radiotherapy is justified. Clinical recurrences at the internal mammary and axillary regions, on the other hand, are uncommon, occurring in less than 5 percent of cases. One exception to this pattern was seen in the Danish postmastectomy radiotherapy randomized trials reported by the Danish Breast Cancer Cooperative Group (Overgaard, Hansen, Overgaard, et al., 1997; Overgaard, Jensen, Overgaard, et al., 1999). In those trials, the axilla was found to be the second most common site of locoregional recurrence (after the chest wall) among patients randomized not to receive

radiotherapy, with 13 percent of patients having an axillary failure as the first failure site. This high failure rate is attributed to a more limited axillary dissection than the procedure typically performed by U.S. surgeons. Due to the rarity of axillary failures in the United States, and the fact that the risk of lymphedema increases with axillary irradiation following surgical dissection, the full axilla is generally not encompassed in the radiotherapy field.

A decision to irradiate the internal mammary nodes is a controversial one. Extended radical mastectomy series have shown that patients with positive axillary nodes are at risk for internal mammary involvement in up to 50 percent of cases. In theory, these cells could serve as a nidus for distant dissemination if left untreated. Despite this concern, no trials to date have shown a significant benefit in overall survival for patients treated in the internal mammary region; a significant benefit, however, has been shown for patients treated for positive axillary nodes and medial lesions (Le, Arriagada, deVathaire, et al., 1990). A large multi-institutional trial sponsored by the European Organization for Research and Treatment of Breast Cancer (EORTC) is currently in progress to assess the benefit of internal mammary (and supraclavicular) radiotherapy in the presence of contemporary systemic therapy. Although it is still unproven whether treatment of these nodes affects survival in the era of aggressive chemotherapy, it is clear that if the internal mammary nodes are to be irradiated, careful planning is critical to minimize cardiac toxicity.

Prior to the publication of reports on the recent randomized trials demonstrating a survival benefit with the addition of postmastectomy radiotherapy (Overgaard, Hansen, Overgaard, et al., 1997; Overgaard, Jensen, Overgaard, et al., 1999; Ragaz, Jackson, Le, et al., 1997), radiotherapy was indicated solely to reduce the risk of locoregional failure in patients deemed to be at high risk, including patients with locally advanced disease and early stage cancers associated with multiple positive nodes (four or more), where the risk of locoregional recurrence is generally 20 percent or more. Recent trials have shown a survival benefit following radiotherapy in all node-positive women, but the degree of benefit is unclear in patients with one to three positive nodes. Part of the dilemma is based upon the discrepancy in the rates of locoregional failure without radiotherapy in those trials in comparison to failure rates reported in American series. The recent report by Recht and colleagues of the patterns of failure found in studies conducted by the Eastern Cooperative Oncology Group notes that the risk of locoregional failure was 13 percent at 10 years in patients with one to three positive nodes (Recht, Gray, Davidson, et al., 1999). Although this is comparable to the 16 percent actuarial rate seen in the British Columbia trial at 10 years (Ragaz, Jackson, Le, et al., 1997), it is strikingly different from the Danish studies, where the crude rates of locoregional recurrence were approximately 30 percent (Overgaard, Hansen, Overgaard, et al., 1997; Overgaard, Jensen, Overgaard, et al., 1999). Based upon these results, the statement produced from the consensus conference convened by the American Society for Therapeutic Radiology and Oncology to address the controversies regarding patient selection for postmastectomy radiotherapy stated that while there was a consensus that patients with four or more positive lymph nodes should receive radiation therapy, the data were less clear for patients with one to three positive nodes (Harris, Halpin-Murphy, McNeese, et al., 1999). A randomized trial was strongly encouraged to study the degree of benefit in women with one to three positive nodes.

Based upon these concerns and recommendations, a trial sponsored by the Southwestern Oncology Group recently began for women with one to three nodes treated with mastectomy and

chemotherapy, with a randomization to locoregional radiotherapy versus observation. Emphasis will be placed upon radiotherapy techniques that minimize potential cardiac toxicity.

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Side Effects, Quality-of-Life Issues, and Tradeoffs in Adjuvant Therapy for Breast Cancer: The Patient Perspective

Amy S. Langer, M.B.A.

In the past decade, increasing utilization of screening mammography and clinical breast examinations has resulted in a stage shift to earlier disease presentation—unfortunately, primarily among insured and higher-income women. This positive public health trend, together with recent significant advances in the variety and effectiveness of systemic therapy options, has produced more favorable outcomes from adjuvant treatment for many patient groups. However, when they have had a recent diagnosis of invasive breast cancer and are still in the initial phase of shock and dismay, most women are unprepared to make the often complex tradeoffs and challenging decisions about adjuvant treatment that rapidly follow initial diagnosis.

Women with early-stage breast cancer are a highly heterogeneous population. They differ not only by disease and demographic characteristics, such as age, culture, language, income, insurance, and employment status, but also by personal responses and circumstances, including partner/family status and available emotional and social support; personal attitudes and values about their breasts, cancer, and disease; the ability to make decisions based on quantitative factors and abstraction; and how they define survival with an "acceptable" or "good" quality of life. Women also have markedly different physical and emotional responses to therapy, both in the manner and degree in which they experience side effects and their sensitivities to any particular side effect, so that an effect of passing annoyance to one woman may be virtually disabling to another.

Science is currently lacking adequate and effective predictive and prognostic factors—tools to accurately project (and monitor, on the micro level) disease response to any one treatment in an individual patient, and to predict her sensitivity to its side effects. Adjuvant therapy for breast cancer has been prescribed based on patient populations—a "macro" approach that overtreats some women who might be cured with less, different, or no therapy, and undertreats others whose disease recurs, with the population of each group only apparent in retrospect. This is only just beginning to change. Significant improvements are yet to be made in individualizing therapy for each woman so that her treatment is most likely to produce maximal disease response and minimal side effects.

Improvements are also needed in methods of educating and communicating about treatment options. Ultimately, improved knowledge about these important aspects will assist women and health care professionals in the shared task of selecting (or rejecting) approaches to adjuvant treatment, taking into account the individual patient's personality, preferences, and priorities, and her attitudes about tradeoffs, side effects, and quality of life.

Adding to these limitations are pressures in the clinic that result in reduced time spent discussing treatment approaches (and clinical trial options) with patients. Oncology professionals are facing economic stressors, a growing patient volume, and additional clinical administrative requirements. While nurses and other healthcare professionals must juggle increased patient volume and additional tasks, the historic job of offering emotional support and practical suggestions, patient education, and information exchange is receiving lower priority. With the growth of the World Wide Web and as cancer and breast cancer Web sites, chatrooms, and other electronic resources multiply, and in the era of direct-to-patient advertisements for oncology products in lay publications and on television, patients have more and varied opportunities to receive information, misinformation, anecdote, and opinion about breast cancer and its treatment.

Patient and lay access to information resources also now includes the same clinical trial directories, medical journal articles, and professional medical meeting real-time reports and abstracts that were until recently the exclusive territory of trained oncology professionals. However, patients and their families need and want authority and guidance about how to use breast cancer education and information safely and well. Consumers require expert assistance to separate fact from myth, chat, and personal stories, and to help them digest and assess the quality and relevance of the huge, often overwhelming volume of medical and treatment information suddenly so available both off- and online.

Meanwhile, many groups of breast cancer patients—those whose native language is not English, and members of lower-income and lower-literacy populations—are being marginalized by an electronic information explosion that so far is of limited value to them, and to which they have limited access. Although government and private support is growing for early breast cancer detection programs among low-income women and special populations, this same cultural competence has not yet widely extended past screening into diagnosis and treatment programs. As a result, when they have the good fortune to experience early diagnosis, studies have shown that state-of-the-art adjuvant treatments for breast cancer are neither offered to, nor chosen by, medically underserved women sufficiently often.

Finally, in an effort to gather insight to assist the patient and her physician in making the best adjuvant therapy decisions for breast cancer in the current clinical era, we should examine the current relevance, value, and utility of the traditionally underfunded, underattended-to studies that exist on the topic of patient decision-making, risk assessment, and choice. The little data there is about individual patient factors and decision-making as it affects adjuvant therapy decisions were collected in a very different era—when many of the improved options for adjuvant treatment and side effects management did not exist, when patients were less informed and participatory, and when there were fewer breast cancer information resources and support and acquisition styles. Quality of life factors and patient decision-making measurements have traditionally been reduced to dry mathematical formulas rather than patient-centered interactive measurements that use tools such as controlled self-assessments over time. With additional funding and advocacy/patient/academic collaboration, this is an area that may require entirely new research approaches.

Impact of Tamoxifen Adjuvant Therapy on Symptoms, Functioning, and Quality of Life

Patricia A. Ganz, M.D.

Tamoxifen has been an integral part of systemic adjuvant therapy for breast cancer patients since the early 1980s, initially being administered primarily to postmenopausal, node-positive patients, and then subsequently to both premenopausal and postmenopausal patients with hormone-receptor-positive, node-negative tumors (Fisher, Costantino, Redmond, et al., 1989). More recently, tamoxifen has been demonstrated to benefit both women with noninvasive breast cancer and women at high risk for breast cancer (Gail, Costantino, Bryant, et al., 1999). Although the toxicities of tamoxifen are mild compared to combination chemotherapeutic regimens, concerns about the side effects of tamoxifen have become more prominent with the increasing use of this agent in women with very early stage disease (or high risk only), where the absolute gains in quantity of life are modest (Fisher, Costantino, Wickerham, et al., 1998). If symptoms are nearly universal with a treatment and its absolute benefits are small, one can begin to question the personal costs of such therapy. This is the current dilemma of women with very early stage breast cancer who must decide whether or not to take tamoxifen.

Everyday Symptoms and Quality of Life Concerns Associated With Tamoxifen

Many women who have received treatment for breast cancer (surgery, radiation therapy, and adjuvant chemotherapy or hormonal therapy) have anecdotally reported a range of symptoms that have been attributed to tamoxifen, including vasomotor symptoms (hot flashes, sweats), weight gain, depression, hair loss, joint pains, fatigue, vaginal dryness, and diminished sexual functioning (Ganz, Rowland, Desmond, et al., 1998). Many of these symptoms could be due to the concurrent effects of premature menopause induced by chemotherapy or the withdrawal of hormone replacement therapy, along with the psychosocial impact of a cancer diagnosis. Although clinicians tend to remember patients for whom the use of tamoxifen seemed to be associated with severe symptoms that had a major impact on quality of life, there are large numbers of other women who have tolerated tamoxifen adjuvant therapy well and experienced no change in quality of life. Therefore, placebo-controlled trials offer the strongest form of evidence for determining whether increased symptoms are attributable to tamoxifen therapy.

The toxicity of adjuvant tamoxifen therapy has been evaluated in two randomized, placebo-controlled trials. In the Wisconsin Tamoxifen Trial (Love, Cameron, Connell, et al., 1991), 140 postmenopausal, node-negative patients were randomly assigned to tamoxifen or a placebo. Using an interviewer-administered questionnaire, patients were asked to evaluate a range of symptoms, overall toxicity, anxiety, and quality of life. Followup occurred over a 24-month period. Key findings included an increase in hot flashes reported by women on tamoxifen (67.2 percent versus 45.4 percent for placebo at 6 months, $p<0.01$), with severe hot flashes in 20.3 percent versus 7.6 percent for placebo at 6 months, $p<0.04$. Gynecological symptoms (vaginal discharge, irritation or bleeding) were more frequent in tamoxifen users (29.7 percent

versus 15.1 percent for placebo at 6 months, $p<0.05$), but these were predominantly mild in severity. There were no differences between the two groups in the symptoms of racing heart, bone pain, joint pain, gastrointestinal distress, nausea, vomiting, sweaty hands, difficulty sleeping, irritability, depression, or fatigue. Finally, there was no adverse effect on quality of life as measured by nonstandardized questionnaires.

The NSABP B-14 trial of tamoxifen in node-negative, estrogen receptor-positive (ER+) pre- and postmenopausal women (Fisher, Costantino, Redmond, et al., 1994) was a much larger double-blind, placebo-controlled trial, with more than 1,400 women in each study group. However, the study obtained no self-reported data on symptoms or quality of life. Nevertheless, detailed toxicity evaluation of this trial demonstrated a pattern of symptoms similar to that found in the Wisconsin trial. Over the course of 5 years of therapy, 64.1 percent of the patients treated with tamoxifen reported hot flashes, compared to 47.7 percent of placebo patients. Vaginal discharge was noted in 29.7 percent of tamoxifen-treated patients, compared to 15.2 percent of placebo patients. There were no significant differences in reports of weight gain, weight loss, fluid retention, nausea and vomiting, or diarrhea. Protocol therapy was discontinued in an equal number of patients in both groups, but in the tamoxifen group there were more withdrawals (about 50 percent) that were attributed to treatment toxicity.

In a recent cross-sectional study of symptoms and quality of life in breast cancer survivors (an average 3 years after diagnosis), Ganz, Roland, Meyerowitz, et al. (1998) used state of the art self-reported measures to evaluate patients according to type of adjuvant therapy. Hot flashes and night sweats were reported significantly more often in survivors taking tamoxifen than in survivors who had not received any adjuvant therapy. The rates were comparable to those in the placebo-controlled trials described above. Vaginal discharge also increased at rates similar to those in the placebo-controlled trials. Other symptoms (vaginal dryness, weight gain, difficulty concentrating, forgetfulness) were not significantly affected by tamoxifen therapy. Importantly, no significant differences in quality of life or depressed mood could be attributed to the use of adjuvant tamoxifen therapy, in spite of significant increases in vasomotor and vaginal symptoms. Most recently, the Breast Cancer Prevention Trial (BCPT), a randomized, double-blind, placebo-controlled study of more than 13,000 healthy high-risk women, found no detrimental effects on mood and on quality of life from tamoxifen therapy, even though vasomotor symptoms and vaginal discharge were significantly increased by the treatment (Day, Ganz, Costantino, et al., 1999).

Impact of Tamoxifen on Sexual Functioning

Research in both healthy women and women with breast cancer demonstrates an age-related decline in sexual functioning. In the BCPT, rates of sexual activity with a partner did not differ by tamoxifen or placebo status, although a subtle decline in sexual activity was noted for both groups across the first 3 years of the trial. In addition, very subtle changes in becoming sexually aroused and difficulty having orgasm were noted in the women treated with tamoxifen. In the recent cross-sectional studies of breast cancer survivors, no significant differences in sexual health and functioning were found between the survivors and healthy postmenopausal women. A detailed study of the predictors of sexual health after breast cancer (Ganz, Desmond, Belin, et al., 1999) found that chemotherapy, and not tamoxifen, was the most significant

treatment-related variable predicting sexual dysfunction, and was associated with a greater risk of vaginal dryness, a symptom not usually related to tamoxifen therapy.

Serious Risks of Tamoxifen Therapy

Women with small tumors in the breast who must decide whether or not to take adjuvant tamoxifen must weigh the other potential consequences of this therapy, such as endometrial cancer, cataracts, blood clots, and strokes. These are rare, however. Although the relative reduction in risk of breast cancer recurrence is uniform across all stages of disease, the absolute benefit decreases in patients with earlier stage disease and very small invasive cancers. The risks of tamoxifen must be balanced against the potential gains in terms of prevention of local and systemic breast cancer recurrence, improved overall survival, and reduction in the risk of contralateral breast cancer. These risks are strongly associated with advancing age, other health conditions, and the presence or absence of a uterus. Data from the BCPT on the relative risk and absolute frequency of these adverse events are useful in discussions with women concerned about the risks of tamoxifen therapy.

Conclusion

The major symptoms attributable to tamoxifen therapy are hot flashes, sweats, and vaginal discharge. Other common symptoms associated with aging and the menopause, such as joint pains, changes in mood, weight gain, and difficulty concentrating, cannot be directly ascribed to tamoxifen therapy, and are more likely the result of the estrogen deficiency associated with menopause. There is no evidence that breast cancer survivors who take tamoxifen have a poorer quality of life or increased risk of depression. Sexual functioning after breast cancer is most often affected by the presence of vaginal dryness, which is not a specific side effect of tamoxifen but is probably the result of age-related estrogen deficiency and possibly an effect of chemotherapy. Although life-threatening risks caused by tamoxifen therapy, including endometrial cancer, blood clots, and strokes are rare, they cannot be ruled out. Women with breast cancer must therefore evaluate carefully all of the risks and benefits of tamoxifen adjuvant therapy before embarking on such treatment.

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Side Effects of Chemotherapy and Combined Chemohormonal Therapy

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The decision to receive chemotherapy (or concurrent chemohormonal therapy) involves careful consideration of both the potential benefits of therapy and the possible risks. The side effects associated with chemotherapy to treat breast cancer are substantial, and include some common short-term effects (usually present during the period of treatment) as well as the possibility of late toxicity. These side effects vary, depending on the specific agents used in the adjuvant regimen as well as the size of the dose and the duration of treatment. There is also considerable variability across individuals, but our ability to predict which patients will have more severe toxicity is very limited. This review will focus on the short- and long-term toxicity seen with the most commonly used adjuvant chemotherapy (and chemohormonal) regimens, including CMF, CAF, CEF, AC, and AC followed by T [C=cyclophosphamide, M=methotrexate, F=fluorouracil, A=doxorubicin, E=epirubicin, and T=paclitaxel].

Short-Term Side Effects

For the purposes of this review, the short-term side effects of chemotherapy occur during the course of treatment and resolve (in some cases gradually) with the completion of therapy. The most common forms of toxicity include emesis (nausea and vomiting), neutropenia with risk of febrile neutropenia, alopecia, mucositis, neuropathy, and fatigue (Fisher, Anderson, Wickerham, et al., 1997; Levine, Bramwell, Pritchard, et al., 1998; Henderson, Berry, Demetri, et al., 1998). With the exception of neuropathy, most side effects resolve promptly upon the completion of treatment. In recent years, fatigue has been recognized as an important toxicity of chemotherapy. Mild to moderate fatigue is frequent with adjuvant chemotherapy, but it has generally not been reported as part of the toxicity assessment in clinical trials. For this reason, it is difficult to compare the severity of fatigue across regimens. Table 1 lists the other side effects rated on a 0, +, ++, and +++ scale, based on the frequency and severity of the toxicity.

Thromboembolic complications can also be seen with chemotherapy regimens (Levine, Gent, Hirsh, et. al., 1988). The risk of thromboembolic events appears to be increased when chemotherapy and hormonal therapy are administered concurrently.

Table 1. Short-term side effects of chemotherapy for breast cancer

	Emesis	Alopecia	Neutropenia	Mucositis	Neuropathy
CMF*	++	++	+	+	0
FAC	+++	+++	+++	++	0
CEF	+++	+++	+++	++	0
AC	+++	+++	++	+	0
AC--T	+++	+++	++	+	+

*In general, toxicity with all intravenous CMF is less than with classic CMF using oral cyclophosphamide.

Long-Term Side Effects

For most patients and clinicians, the long-term side effects of chemotherapy are of greater concern than the acute short-term effects (Burstein, Winer, 2000). Among the late or chronic effects of chemotherapy, those of greatest concern include (1) premature menopause; (2) weight gain; (3) cardiac toxicity from anthracyclines; (4) secondary leukemia; and (5) cognitive dysfunction. Each of these late effects is considered separately.

Premature Menopause

For premenopausal women with breast cancer, the possibility of experiencing treatment-induced ovarian failure is a major concern (Burstein, Winer, 2000; Bines, Oleske, Cobleigh, 1996). It is beyond the scope of this review to comment on the potential benefits of ovarian failure in relation to cancer recurrence. There is little question, however, that premature ovarian failure results in a number of undesired consequences, including infertility, sexual difficulties, accelerated bone loss, and increased risk of vascular disease. The risk of ovarian failure with chemotherapy is related to the age of the woman, the specific chemotherapy agents used, and the cumulative dose. Cyclophosphamide and doxorubicin are among the agents most often associated with ovarian failure, although a treatment course limited to four cycles of AC is more often associated with preservation of ovarian function than either 6 months of CMF or FAC. Some women will experience periods of ovarian suppression during the course of treatment and in the months following therapy, with restoration of ovarian function after a variable time interval. To what extent a course of chemotherapy may decrease fertility in women who maintain or resume regular menstrual cycles after treatment is unknown. Also unknown is whether women who complete chemotherapy with intact ovarian function will ultimately experience menopause at a younger age than they would have in the absence of chemotherapy.

Weight Gain

Weight gain is a well-recognized complication of chemotherapy (Demark-Wahnefried, Winer, Rimer, 1993). In general, weight gain has been more pronounced in premenopausal than in postmenopausal women. The mechanism of weight gain is uncertain, but it does not appear to be a consequence of excess intake. It is unclear to what extent long-term weight gain is a problem after a course of chemotherapy. To what extent weight gain can be modified through behavioral intervention is also unknown.

Cardiac Dysfunction

The widespread use of anthracyclines has raised concern about the potential for cardiac dysfunction following adjuvant therapy. In most doxorubicin-containing regimens, the cumulative dose of doxorubicin is in the range of 240-360 mg/M^2. With these cumulative doses, the risk of clinical congestive heart failure following therapy is thought to be less than 1 percent (Shan, Lincoff, Young, 1996; Valagussa, Zambetti, Biasi, et al., 1994). There are rare patients who present with congestive heart failure with doses in this range. Although higher cumulative doses of epirubicin are used in epirubicin-containing regimens, this anthracycline is less cardiotoxic than doxorubicin on a mg to mg basis. To date, long-term followup of patients treated with anthracyclines in the adjuvant setting is limited. In a recent report, more than 300 women who were a median of 10.8 years from diagnosis underwent cardiac evaluation, including an echocardiogram (Gianni, Zambetti, Moliterni, 1999). Women who had received anthracyclines in the adjuvant setting did not have clinical symptoms of cardiac dysfunction, but a higher proportion of women who had received anthracyclines compared to those who had CMF alone were reported to have a borderline or decreased left ventricular ejection fraction.

Secondary Leukemia

Breast cancer patients treated with adjuvant chemotherapy have a slightly increased risk of leukemia. With CMF-type regimens, the increased risk appears to be negligible (Curtis, Boice, Stoval, et al., 1992; Tallman, Gray, Bennett, et al., 1995). Anthracycline-based regimens are associated with a greater risk, though still of relatively small magnitude. In a series of patients treated with FAC at the M.D. Anderson Cancer Center, the risk of leukemia at 10 years was estimated to be 1.5 percent. The median time to diagnosis of leukemia was 66 months (Diamandidou, Buzdar, Smith, et al., 1996). Recent reports from the NSABP (B-22 and B-25) have also indicated an increased risk of acute myelogenous leukemia and myelodysplastic syndrome in women treated with AC (standard dose doxorubicin with standard or dose-intensified cyclophosphamide) (Fisher, Anderson, Wickerham, et al., 1997; Fisher, Anderson, DeCillis, et al., 1999).

Cognitive Dysfunction

Recent reports have suggested that chemotherapy—both high dose and standard dose therapy—may be associated with cognitive dysfunction (Brezden, Phillips, Abdolell, et al., 2000; van Dam, Schagen, Muller, et al., 1998). The studies have not been definitive, however, and additional research is needed to determine if cognitive difficulties are a consequence of adjuvant chemotherapy.

Summary

In summary, adjuvant chemotherapy (with or without concurrent hormonal therapy) is associated with a range of acute forms of toxicity which generally resolve once treatment has been completed. With the exception of premature menopause, long-term toxicity is generally quite rare. However, these uncommon late effects need to be considered in making decisions about adjuvant therapy, particularly when a patient is at low risk of disease recurrence and the absolute benefit of treatment is of small magnitude. Further research is needed to characterize fully the spectrum of late forms of toxicity following adjuvant chemotherapy.

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Decision-Making Process–Communicating Risks/Benefits: Is There an Ideal Technique?

Mark Norman Levine, M.D., and Timothy J. Whelan, M.Sc.

In recent years there have been major advances in the treatment of early-stage breast cancer, but the decisions a patient must make about treatment are often difficult and complex. In the past, physicians tended to make decisions for patients with little input from patients. Various studies, however, have suggested problems in that traditional decisionmaking process, particularly with regard to the transfer of information from the physician to the breast cancer patient (Siminoff, Fetting, Abeloff, 1989).

Many patients have begun seeking more information about their disease and have shown a desire to be actively involved in decisions about their treatment. Researchers and clinicians have responded by investigating ways of transferring information in ways more helpful to patients. Decisionmaking aids have been defined as "interventions designed to help people make specific and deliberative choices among options by providing information on the options and outcomes relevant to the person's health status" (O'Connor, Fiset, DeGrasse, et al., 1999). Such aids now take the form of printed materials, computer-based programs, video programs, audio-guided workbooks, and decision boards.

In general, the patient/physician relationship involves several stages of exchange of information, deliberation, and decisionmaking (Charles, Whelan, Gafni, 1999). At one extreme is a paternalistic model, where information flows in one direction from the doctor to the patient and the doctor alone makes the decision. At the other extreme is the informed model, where the patient alone makes the decision. The alternative to these models is the shared model, in which the doctor and patient reach agreement together at all stages of the decisionmaking process. There is a two-way exchange of information in which the doctor and patient express treatment preferences, discuss them, and come to agreement on which treatment will be used.

O'Connor and colleagues recently conducted a systematic review of decisionmaking aids in the treatment of various cancers (O'Connor, Fiset, DeGrasse, et al., 1999) and other conditions (O'Connor, Rostom, Fiset, et al., 1999). Studies evaluating these aids have found that they are acceptable to patients and do not impact on patient satisfaction.

There have been relatively few studies of decisionmaking aids for women with early-stage breast cancer. In a trial by Goel and colleagues, women faced with a decision regarding surgery for breast cancer were randomly directed to an information pamphlet or an audio-guided workbook (Goel, Sawka, Thiel, et al., 1998). The study detected no differences in knowledge or decisional conflict between the two groups.

The decision board was initially developed to help women with node-negative breast cancer decide whether or not to receive adjuvant chemotherapy (Levine, Gafni, Markham, et al., 1992). It was found to be both acceptable and helpful in decisionmaking. A cohort study on the

use of a decision board by patients deciding whether or not to undergo postlumpectomy radiation found that the process improved patient knowledge and facilitated shared decisionmaking (Whelan, Levine, Gafni, et al., 1995). In another study, Whelan and colleagues found that the use of a decision board by women deciding between lumpectomy and mastectomy led to a decrease in the lumpectomy rate (Whelan, Levine, Gafni, et al., 1999). Randomized trials are currently ongoing to evaluate the decision board process in deciding on lumpectomy versus mastectomy, and on adjuvant chemotherapy for node-negative and node-positive breast cancer.

In conclusion, both patients and physicians find decision aids helpful, but there have been relatively few studies of their use by patients with early-stage breast cancer. Further research is needed to determine whether decision aids can improve such outcomes as satisfaction, downstream quality of life, and unexplained practice variation. Research is also required to determine whether particular decisionmaking aids are better than others for a particular patient group or for different types of medical intervention.

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Assessing Individual Benefit

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Three questions are relevant to the decision to give or withhold any particular treatment, including adjuvant systemic therapy for early breast cancer:

1. **Is there a benefit (beyond the play of chance)?**

   This is essentially a statistical question to be answered by reference to appropriate randomized clinical trials. There have been many trials involving patients with early breast cancer, and the answer is expressed in terms of the standard test of significance. If the answer is yes, the next question arises.

2. **How large is the benefit?**

   Again, the answer to the question is statistical, but it can be more difficult to answer than the first question. Measures of the size of the benefit include reduction in the odds of death or relapse, differences in the probability of survival to a certain time after treatment, and differences in median survival rates. Estimates of these may be available from clinical trials, but it can be a matter of judgment whether to use average values or values derived from trials involving more specific subgroups. Once that question has been answered, one question remains.

3. **Is it worth it (for this patient with this tumor)?**

   The answer to this question is not statistical and involves the preference of the patient in light of estimates of the morbidity of a treatment. Individual morbidity is difficult to predict, and after a patient has undergone therapy the question becomes academic. Only such patients, however, can provide value judgments based on actual experience of the therapy.

Several studies have tried to establish benchmarks, based on the experience of one group of patients. Our initial study, conducted between November 1986 and December 1987, involved women who had received then-standard cytotoxic chemotherapy of at least three 28-day cycles of treatment (Coates, Simes, 1992). These patients were interviewed to determine the degree of benefit that, in their view, would make such treatment worthwhile. Of 129 patients considered for participation, 104 patients completed the interview, which was conducted at least 3 months after completion of chemotherapy by two observers with no connection to the treatment. The basic goal was to establish the patients' opinion of what additional period of survival would be

worthwhile to justify the adverse experience of the treatment they had received. Patients were presented with hypothetical scenarios which took a general form along these lines:

> "Suppose that without treatment you would live 5 years. Based on your experience of chemotherapy, what period of survival would make 6 months of treatment worthwhile?"

A similar scenario was then used to establish equivalence to an expectation of 15 years of survival without treatment, which perhaps was an appropriate expectation for low-risk, node-negative patients. Survival questions were similar to the time trade-off approach but expressed the outcome of treatment in terms of the percentage chance of remaining alive after 5 years.

The major finding was that a large majority of the patients said that relatively modest improvements in the duration of survival or in the percentage chance of 5-year survival would justify their 6 months of treatment. This was true for both the optimistic scenarios (untreated survival of 15 years or 5-year survival of treatment at 85 percent) and in the less favorable (untreated survival of 5 years or 5-year survival of treatment at 65 percent). Most of the patients were inclined to accept treatment in return for an additional year of survival. This was true for both an extension from 5 years to 6 years (77 percent acceptance) and from 15 years to 16 years (61 percent acceptance). When asked about survival percentages, patients were willing to be treated for a 2 percent improvement in survival probability, either from 85 percent to 87 percent (54 percent acceptance) or from 65 percent to 67 percent (53 percent acceptance). In the light of a recent overview (EBCTCG, 1998), differences of this magnitude appear to be reasonably achievable for many patient groups receiving adjuvant cytotoxic therapy. Discussing the proportion of women with treatment experience who found it acceptable in exchange for a realistically achievable gain in survival may assist an untreated woman in reaching a decision about whether or not to undergo treatment herself.

Similar results have been reported by others. Slevin and colleagues interviewed a group of British patients with a variety of tumor types and found that they were much more ready to accept intensive treatment than controls or health professionals (Slevin, Stubbs, Plant, et al., 1990). Median required benefits for the hypothetical intensive treatment were a 1 percent chance of cure or 12 months prolongation of life, findings rather similar to those expressed by the breast cancer patients. Similarly, Bremnes and colleagues offered a hypothetical toxic regimen to Norwegian patients and found that patients, especially younger patients, were significantly more likely to accept treatment than controls or health professionals (Bremnes, Andersen, Wist, 1995; Coates, 1995). More recently, Lindley and colleagues found that more than 65 percent of the patients in their study who had completed adjuvant therapy for breast cancer would accept 6 months of chemotherapy for a 5 percent increase in likelihood of cure (Lindley, Vasa, Sawyer, et al., 1998). In another study, cisplatin-treated lung cancer patients showed a high percentage willing to accept even toxic therapy for a survival gain of 1 year, though that may be a less realistic hope in such patients (Silvestri, Pritchard, Welch, 1998).

Similar studies are under way in Britain to examine the preferences of patients who have received various endocrine therapies, and we are repeating our initial study to determine the preferences of those exposed to more recent therapies and supportive care in early breast cancer. Overall, these studies clearly show that patients' views cannot be determined by interviewing

surrogates, and that the benefit demanded by most patients to justify therapy is modest and within the capabilities of current adjuvant systemic therapy for early breast cancer.

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