Adjuvant Therapy for Breast Cancer: Recommendations for Management Based on Consensus Review and Recent Clinical Trials

BETTY A. MINCEY,a,b FRANCES M. PALMIERI,b EDITH A. PEREZb,c

aDivision of General Internal Medicine, bMultidisciplinary Breast Clinic, cDivision of Hematology and Oncology, Mayo Clinic, Jacksonville, Florida, USA

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ABSTRACT

Determining the optimal individual adjuvant systemic therapy for breast cancer patients is a challenging undertaking because it requires translating data from clinical trials that have involved thousands of patients into a highly individualized, risk-adjusted approach for the patient at hand. Choosing adjuvant therapy for women with breast cancer includes consideration of four issues: A) evaluation of risk of relapse; B) extrapolation of results from clinical trials; C) therapeutic ratio, and D) the patient’s preferences following a thorough discussion with her physician. Data from recently completed phase III adjuvant trials and worldwide consensus conferences document the benefits of adjuvant therapy in improving disease-free survival and overall survival for patients diagnosed with invasive breast cancer >1.0 cm in size. The benefits of hormonal therapy are clear, but limited to patients with estrogen receptor-positive breast cancer. Anthracyclines lead to improved outcomes compared with nonanthracycline regimens. Taxanes appear to improve disease-free survival in patients with node-positive disease, although longer follow-up is required to assess their impact on overall survival. Some countries have reported a reduction in the mortality rate from breast cancer over the past several years. The improved survival rate is due, at least in part, to the use of adjuvant systemic therapy. Ongoing studies are evaluating targeted therapies, with the potential of remarkably improving patient outcome. The Oncologist 2002;7:246-250

Correspondence: Edith A. Perez, M.D., Division of Hematology and Oncology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, Florida 32224, USA. Telephone: 904-953-7283; Fax: 904-953-2315; e-mail: perez.edith@mayo.edu

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INTRODUCTION

Appropriate local therapy remains the cornerstone of treatment for patients with nonmetastatic breast cancer. Systemic chemotherapy, with or without hormonal therapy based on the biological characteristics of the tumor, is the current standard of treatment for patients with node-positive breast cancer, and for a large portion of those with node-negative disease and invasive tumors measuring >1.0 cm. Ultimately, the success of adjuvant therapy will depend not only on optimizing current regimens, but also on exploring new therapeutic targets, improving the understanding of individual tumor and patient characteristics that influence treatment selection and outcome, critical analysis and integration of data, consensus building, and education regarding the results of these analyses.

A large amount of data has been accumulated over the last few years, helping us to better understand the utilization of ovarian ablation, hormonal therapy, and chemotherapy, as well as local treatments for patients with early breast cancer. Some of these data were discussed as part of the Early Breast Cancer Trialists’ Group (EBCTG) conferences in 1998 and 2000 [1, 2], the 2000 National Institutes of Health (NIH) Consensus Conference [3], and the 2001 7th St. Gallen meeting [4]. The overall results from the studies discussed are consistent with significant improvements in disease-free and overall survival for all groups of patients: pre- or postmenopausal, node positive or negative.

PROGNOSTIC AND PREDICTIVE FACTORS IN THE ADJUVANT SETTING

Selection of adjuvant systemic therapy is based on patient characteristics and prognostic and predictive factors. Nodal status, tumor size, histologic type, grade, hormone-receptor status, and age are recommended as prognostic factors for decisions regarding therapy. Hormonal receptor status is recommended as predictive of response to tamoxifen, and now also to aromatase inhibitors. The role of HER2 as both prognostic and predictive is still debated, but increasing amounts of data support its value as both [5-7]. The data supporting its prognostic value for patients with node-positive breast cancer are clearer, and data are getting stronger in support of its value as a predictor of benefit from anthracyclines and perhaps taxanes. Three difficulties have complicated the evaluation of HER2. These are: the lack of consistency regarding methodology for testing; problems with concordance of testing between local and central laboratories; and the lack of statistical power in the studies conducted to definitively address this potentially important discriminant of prognosis and response. The role of novel technologies, such as gene microarrays and proteomics for identifying prognostic and predictive factors, awaits results from rigorously designed prospective clinical trials.

The St. Gallen’s conference meeting panel recommended that patients be divided into risk categories to help make decisions regarding adjuvant treatment. Those considered to be at minimal risk of recurrence included patients older than 35 years whose tumors were node negative with a tumor size <2.0 cm and of grade 1 histologically. Tamoxifen or no therapy was recommended for those patients. Patients with average or high risk were: those aged less than 35; those whose tumors were estrogen and progesterone receptor-negative; those with grade 2-3 tumors, regardless of size; and those with tumors >2.0 cm, independent of estrogen-receptor status. Recommendations for these patients included various permutations of tamoxifen and/or chemotherapy.

LOCAL THERAPY

Radiation therapy was recommended to reduce local recurrence for patients who undergo lumpectomy or quadrantectomy, and also for those who undergo mastectomy but have four or more involved axillary lymph nodes. Radiation was also recommended for patients who undergo mastectomy for tumors measuring >5.0 cm.

HORMONAL THERAPY

Ovarian ablation was found to be similar to older chemotherapy regimens, such as cyclophosphamide methotrexate and fluorouracil (CMF), for premenopausal women. The role of ovarian ablation in combination with chemotherapy remains a matter for further study. Trials to better evaluate ovarian ablation are in the planning stages, including studies with premenopausal patients who have not received chemotherapy or those who remain premenopausal after receiving systemic chemotherapy. The role of aromatase inhibitors instead of tamoxifen for patients who undergo ovarian ablation will be important in view of the preliminary data from the anastrozole, tamoxifen, alone or in combination (ATAC) trial presented in December 2001 [8].

The different consensus conferences recommended tamoxifen for 5 years for patients with estrogen receptor-positive breast cancer whose tumors measured >1.0 cm, independent of menopausal state or lymph-node status. This was based on large amounts of data, including the findings from the EBCTG demonstrating a highly statistically significant 47% reduction in annual odds of recurrence and a 26% reduction in annual odds of death for patients with estrogen receptor-positive tumors receiving 5 years of tamoxifen [2]. However, these conclusions were reached before the ATAC results alluded to above became available. The ATAC study demonstrated a small, but statistically significant, improvement in disease-free survival.
for postmenopausal patients with resected breast cancer who received anastrozole instead of tamoxifen, but not for the concurrent use of tamoxifen with anastrozole [8].

There was a clear consensus that tamoxifen should not be recommended for patients with estrogen receptor-negative breast cancer. This recommendation is supported not only by the meta-analyses, but specifically by data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-23 and the Intergroup study INT102 [9, 10]. These two studies not only failed to demonstrate benefit for tamoxifen in patients with estrogen receptor-negative breast cancer, but also did not demonstrate that tamoxifen decreased contralateral breast cancer in patients with primary estrogen receptor-negative disease. Moreover, the Intergroup INT102 study demonstrated an apparently detrimental effect of tamoxifen in premenopausal patients with estrogen receptor-negative breast cancer. The presence or absence of HER2 expression should not be a determinant of whether to use hormonal therapy, based on currently available data.

Regarding patient follow-up while on tamoxifen, neither routine transvaginal ultrasound nor endometrial biopsies are recommended as screening procedures. The utilization of alternative hormonal treatments, such as aromatase inhibitors, in postmenopausal patients who have completed adjuvant tamoxifen is being investigated in ongoing clinical trials.

**CHEMOTHERAPY**

The EBCTG meta-analysis published in 1998, after review of adjuvant therapy trials that started before 1990, reported that chemotherapy reduced the annual odds of recurrence by 40% in patients younger than 50 years of age with estrogen receptor-negative tumors and by 33% in those with estrogen receptor-positive disease [1]. However, this apparent difference, based on receptor status, was not statistically significant. Similarly, there was a 30% reduction in the annual odds of recurrence in patients older than 50 with estrogen receptor-negative tumors and an 18% reduction in those with estrogen receptor-positive tumors. Moreover, irrespective of hormonal receptor status, there was a statistically significant reduction in annual odds of death for both women under 50 (27% reduction, 2-sided \( p < 0.00001 \)) and for those aged 50-69 (11% reduction, 2-sided \( p = 0.00001 \)). For the overall group of women (irrespective of age), polychemotherapy significantly reduced the annual odds of recurrence and death by 24% and 15%, respectively. The data from the analysis of trials starting prior to 1995 (before the completion of the new trials evaluating taxanes) and presented at the October 2000 meeting have not yet been published.

The 2000 NIH Consensus Conference addressed several issues regarding chemotherapy worthy of mention. It was recommended that the majority of women should receive systemic chemotherapy for four to six courses. Randomized trials of the same chemotherapy given four or six times have not been completed, so it was difficult to issue a definitive statement regarding the exact number of months or cycles for which chemotherapy should be given. But, in general, it was felt that 6 months of treatment was enough, and that some patients may be able to be treated for less than that. One of the challenges of this strategy is that most of the studies comparing an equal number of cycles of anthracycline with nonanthracycline regimens demonstrate a benefit for anthracyclines, and one study demonstrated that four cycles of adriamycin and cyclophosphamide (AC) were equivalent to six cycles of oral CMF. Thus, by inference, it may be that four cycles of anthracyclines are actually inferior to six cycles of the same anthracycline. The U.S. Breast Intergroup will test this question in a large randomized trial.

The use of anthracyclines resulted in a survival benefit when compared with CMF-like regimens, with improvement in the annual odds of recurrence and death of 11% and 12%, respectively. The integration of tamoxifen with chemotherapy was not discussed at these consensus meetings, but data from studies by two cooperative groups (North American Breast Intergroup and the Spanish group GEICAM) were presented at the 2002 ASCO meeting. The practice of the U.S. Breast Intergroup has been to complete chemotherapy and then initiate tamoxifen, based on preclinical data and the potential for increased thromboembolic events with concurrent use of these agents. Data from the GEICAM trial have short follow-up, but those from the Intergroup trial demonstrate a statistically significant improvement in disease-free survival at 8 years using sequential chemotherapy followed by tamoxifen compared to the concurrent use of these agents [11-13].

The use of taxanes was not strongly recommended due to the short follow-up of the few studies reported so far. However, the small but statistically significant improvement in disease-free survival and the trend for improved survival for patients receiving paclitaxel after AC instead of AC alone as part of the Cancer and Leukemia Group B 9344 Intergroup trial was thoroughly discussed [14]. The NSABP B-28 trial was reported with only 34 months of follow-up at the NIH Consensus Conference. The short follow-up time, added to the fact that 62% of patients enrolled had one to three involved axillary lymph nodes, 85% received tamoxifen, and 25% could not complete the planned four doses of taxane due to toxicity, make it impossible to utilize these early data to reach conclusions regarding the 10 or 20 year potential impact.
of four cycles of taxane following anthracycline-based treatment as adjuvant therapy for breast cancer. Lastly, preliminary data from the BCIRG 001 trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) to FAC (5-fluorouracil, doxorubicin, cyclophosphamide) demonstrate improvements in disease-free survival, for the TAC-treated patients, at a median follow up time of 33 months. Follow-up of these studies and review of pending data from more than 10 already completed or soon to be completed studies of taxane versus nontaxane regimens will allow for a clearer understanding of their role in the adjuvant setting. At this time, it is important to remember that studies in the metastatic setting have not demonstrated differential benefit of taxanes based on the tumor’s receptor status. Longer follow-up of patients receiving tamoxifen or another hormonal therapy will be necessary for valid subgroup analyses based on hormonal receptors. In other words, the benefit of taxanes based on estrogen-receptor status may be incorrectly interpreted if the analysis occurs too early in relationship to the natural history of the disease. At this time, there are no data to suggest the benefit of taxanes in patients with node-negative breast cancer, but studies are ongoing to answer this question.

There is no evidence that dose-intensive regimens requiring colony growth-stimulating factor support or stem cell transplantation result in improved outcomes.

**Targeted Therapies**

An exciting area of research is the incorporation of targeted treatments in the adjuvant setting [5, 6, 15]. However, none are ready for general use at this time. The only targeted therapy approved for use in the metastatic setting, other than anti-estrogens, is trastuzumab, an agent that is now being evaluated in four well-planned worldwide adjuvant trials conducted by cooperative groups. Completion of recruitment and analysis of the data that may demonstrate a benefit of this anti-HER2 monoclonal antibody when added to chemotherapy could be a major advance in the treatment of patients at high risk of relapse following resection of invasive breast cancer. Additionally, all of these studies include the prospective collection of tumor specimens, which will assist in the understanding of the biology of breast cancer.

**Physician-Patient Communication**

The physician should be able to communicate to the patient that survival improvements following the diagnosis of breast cancer are partly due to the use of effective adjuvant therapy. This discussion should include that determining the best strategy for an individual patient is dependent upon an objective evaluation of prognosis (based on patient and tumor characteristics) and a careful evaluation of the therapeutic ratio of different regimens. The concepts of yearly odds of recurrence and overall recurrence in the context of no therapy or different systemic treatments should be part of the discussion, so that the patient can understand the rationale for selecting among different options. Additionally, it is important for patients to be informed about the concepts of proportional benefit (percentage reduction in the odds of recurrence or death using different strategies) and absolute benefit (number of recurrences or deaths avoided per 100 women treated). The fact that breast cancer is, in essence, a treatable disease, that advances have been made to improve the cure rate while minimizing toxicity through the conduct of clinical trials, and that new approaches continue to be tested in clinical studies (with careful oversight) is worthy information to provide to patients. Discussion of clinical trials in which the individual patient may be able to consider participating could be one of the fastest ways to improve adjuvant therapies and the cure rate for this disease.

**Conclusions**

The survival of women with breast cancer has been improving in most countries. The reason for this change is a combination of earlier diagnosis, better medical care in general, and appropriate administration of systemic treatments following resection of breast cancer. Development of, recruitment to, and analysis of rigorous, carefully conducted, scientifically well-designed and ethical trials will be the best way to improve adjuvant therapy in the years to come.

**Acknowledgments**


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