Special Article

Adjuvant Systemic Therapy for Early Breast Cancer: Progress and Controversies

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The diagnosis and management of breast cancer have changed considerably over the past 4 decades. The introduction of adjuvant endocrine therapy (ovarian ablation) and adjuvant chemotherapy in the 1960s was a paradigm-changing event, based on improved understanding of the natural history of human breast cancer and the increased realization that micrometastases were in existence in most patients at the time of initial diagnosis (1, 2). The initial steps were timid, and the first few clinical trials were substantially underpowered to answer with any degree of certainty whether "prophylactic" chemotherapy or endocrine therapy could reduce the odds of recurrence and mortality in patients with primary breast cancer. Although most North American oncologists accepted adjuvant chemotherapy for premenopausal patients with axillary lymph node-positive breast cancer by the late 1970s, marked controversy characterized the use of this treatment for other subgroups of patients with primary breast cancer. Adjuvant endocrine therapy was also viewed with much skepticism. The Early Breast Cancer Trialists' Collaborative Group established a database of all randomized clinical trials (whether published or not) of primary breast cancer. Meta-analyses of all available data explored the effect of systemic and locoregional therapies on odds of recurrence and mortality. These meta-analyses were conducted at 5-year intervals, starting in 1985, and have contributed immensely to the general acceptance of various forms of adjuvant chemotherapy as standard treatment (3-8). However, some of the conclusions of the meta-analyses have been questioned on the basis of biological mechanisms, whereas others are in conflict with the results of some of the largest multicenter clinical trials.

To resolve controversies and summarize accepted advances in the field, the NIH has organized over the past 3 decades several Consensus Development Conferences about the management of primary breast cancer (9, 10). The most recent one, held in early November 2000 at the NIH campus, demonstrated that additional progress had been made, and as expected, new controversies replaced old ones. An independent panel of experts in multidisciplinary clinical trials in oncology reviewed information from clinical trials presented by breast cancer experts and thought leaders. At the end of the meeting, the panel issued a comprehensive, evidence-based report on the status of adjuvant chemotherapy. Since the stated goal of the conference was to review adjuvant systemic therapy, a number of other, ongoing controversies related to the management of early breast cancer (i.e., sentinel lymph node mapping) were not addressed. Let's review both areas of accepted progress and remaining controversy.

Prognostic and Predictive Factors

After decades of laboratory and clinical investigation, those factors found to be clinically useful and reproducible in predicting risk of recurrence or death include the presence and number of positive axillary lymph nodes, pathological size of the primary tumor, and histological type and grade. Several of these are used jointly in the Nottingham prognostic index, which has been validated prospectively by several investigators or groups (11). Age, race, and steroid hormone receptor status were also found to have prognostic significance. Other factors commonly reported in clinical trials have not been shown consistently to have independent prognostic value or have not been validated in appropriately designed clinical trials.

Specifically, the controversy about the validation of HER-2 as an independent prognostic marker persists. Other biological parameters predict response or resistance to specific therapies. Among these, estrogen and progesterone receptor status predicts responsiveness to endocrine interventions, whereas HER-2/new status indicates the likelihood of benefit from trastuzumab therapy.

Controversy continues about the clinical utility of measures of tumor cell proliferation, assessment of neoangiogenesis, protease expression, or molecular markers, such as p53 mutations and BCL-2 expression. Proteomics and microarray technologies show great promise but have, as yet, no role in the management of breast cancer.

Adjuvant Hormone Therapy

This consensus conference reaffirmed the value of endocrine therapy with ovarian ablation (whether surgical, chemical, or radiation induced) in the reduction of risk of recurrence or death for premenopausal patients (6). On the basis of multiple randomized trials, the benefits from this intervention appear similar to those of adjuvant chemotherapy and persist even 15 years beyond the onset of ovarian ablation (12). The benefit of ovarian ablation appears limited to premenopausal women with
The panel resoundingly endorsed adjuvant tamoxifen. Emerging evidence not only confirmed the value of tamoxifen in reducing risk of recurrence and death but also demonstrated that the effects of this intervention persist 10 and probably 15 years beyond diagnosis (8). On the basis of available data, the optimal duration of tamoxifen therapy appears to be 5 years. The most recent meta-analysis and several large, modern randomized clinical trials demonstrated that the efficacy of tamoxifen is limited entirely to women with estrogen receptor-positive breast cancer. Furthermore, tamoxifen does not reduce the incidence of second primary breast cancers in patients diagnosed to have an estrogen receptor-negative primary tumor. These findings terminated the controversy of using tamoxifen in premenopausal patients with estrogen receptor-positive tumors (tamoxifen treatment indicated) or postmenopausal women with estrogen receptor-negative tumors (tamoxifen treatment not indicated).

Additional data demonstrated that, for patients of any age with estrogen receptor-positive breast cancer, the combination of tamoxifen and chemotherapy provides greater benefits than either treatment alone (8). Whether the combination of chemotherapy with any form of ovarian ablation is superior to chemotherapy alone (or ovarian ablation alone or tamoxifen alone) remains to be demonstrated and is the subject of intense study.

**Adjuvant Chemotherapy**

The panel endorsed the notion that most patients with primary breast cancer, regardless of age, hormone receptor status, or the presence of axillary lymph node involvement, benefit from adjuvant chemotherapy. The evidence presented supported the superiority of combination chemotherapy over single-agent treatment and the use of anthracycline-based therapy as the treatment of choice for most patients (7). The use of doxorubicin or epirubicin in combination with other agents provided greater benefit than combinations without anthracyclines. Although the AC regimen has been readily adopted in North America because of its ease of administration, there is no evidence that this regimen is any better than CMF or that it is equivalent to more widely tested combinations, such as fluorouracil/Adriamycin/cyclophosphamide, cyclophosphamide/Adriamycin/fluorouracil, or fluorouracil/epirubicin/cyclophosphamide each of which has been shown to be superior to the classical CMF regimen.

Patients <50 years of age (most of whom are premenopausal) appeared to derive greater benefit from adjuvant chemotherapy than women in older age groups (7). Because adjuvant chemotherapy regimens in use today produce persistent amenorrhea in almost two-thirds of premenopausal patients, these results suggest that chemotherapy has both an endocrine and a cytotoxic effect in younger women, whereas it is only a cytotoxic agent for postmenopausal patients (13–15). Because the magnitude of benefit is more modest for women >50 years of age, the absolute benefit for older women with relatively good prognostic primary breast cancers might be as small as 1–3%. Data from randomized trials also suggested that, when using a single combination, four to six cycles of therapy provide optimal results; shorter treatment durations might be less effective. Fixed cross-over regimens using two different combinations under evaluation today require longer durations of treatment (16, 17).

The role of taxanes in the adjuvant therapy of breast cancer was discussed extensively. Two consecutive analyses of a large randomized trial (Cancer and Leukemia Group B 9344) designed to test whether four cycles of paclitaxel after four cycles of AC improved the results of four cycles of AC demonstrated a significant reduction in the odds of recurrence and death for the paclitaxel-containing arm (17). The results of the third analysis of this trial (presented at the Consensus Development Conference) showed the magnitude of the benefit had decreased but remained significant. Two other randomized trials (National Surgical Adjuvant Breast and Bowel Project and M. D. Anderson Cancer Center) also designed to test the role of taxanes in the adjuvant chemotherapy of breast cancer, failed to show a significant advantage for the paclitaxel group at the time of the analysis, but longer follow-up is needed because the early results are consistent with the results of Cancer and Leukemia Group B 9344. Thus, whereas the Food and Drug Administration approved the use of paclitaxel for adjuvant therapy of node-positive breast cancer, the Consensus Panel determined that the evidence in support of the taxanes was inconclusive and that additional data were necessary for definitive statements with regard to the role of these drugs in adjuvant therapy.

Dose and dose-intensive therapy were reviewed in detail. The available evidence suggested no definitive benefit from increasing the dose or dose intensity of commonly used agents beyond the doses tolerated without growth factor or hematopoietic stem cell support (18).

Substantial controversy remains about which groups of patients should not receive adjuvant systemic therapy (19). As a rule of thumb, the panel endorsed adjuvant systemic therapy for women with positive axillary lymph nodes or tumors >1 cm in largest diameter, recognizing that some patients with smaller, node-negative tumors might want to receive systemic therapy to maximize their chance of remaining relapse free. There was considerable discussion about benefit-risk ratios and sharing detailed information about prognosis and benefits of therapy with patients, as well as additional research with regard to long-term toxicity and quality of life issues. The panel also heard evidence that showed that many patients would be willing to receive currently used adjuvant systemic treatments even to gain minimal or marginal benefits in survival (~1%). However, for very low-risk patients, the probability of severe or life-threatening toxicity from chemotherapy might match, and in some instances exceed, the probability of survival benefit. For these patients, adjuvant chemotherapy does not produce a net benefit and should not be recommended.

**Postmastectomy Radiotherapy**

The results of multiple randomized trials and several meta-analyses of the data demonstrated that radiotherapy markedly reduces the risk of locoregional failure after mastectomy (20–

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3 The abbreviations used are: CMF, cyclophosphamide/methotrexate/fluorouracil; AC, Adriamycin/cyclophosphamide.
In addition, these studies point out a modest but significant reduction in breast cancer mortality associated with radiotherapy. The overview suggested that this survival advantage was matched by a similar rate of cardiovascular mortality thought to be associated with chest wall radiotherapy (24). More recent studies, purportedly using modern radiotherapy techniques, have not shown (as yet) an increased rate of radiotherapy-related mortality (25–27). The panel concluded that, for patients in the high-risk group (=4 positive lymph nodes or those with T2, T3 tumors) postmastectomy radiotherapy represented the standard of care, whereas for patients with lower calculated risk of recurrence, additional research was needed.

The optimal sequence of administration of adjuvant therapies was also discussed. Although existing evidence is not totally conclusive, it suggests that for most patients, adjuvant chemotherapy should be administered before the initiation of radiotherapy (28).

Role of Side Effects and Quality of Life in Selection of Adjuvant Systemic Therapy

Several presentations pointed out the frequency and type of acute side effects and long-term toxicity of various adjuvant therapies (15, 29–31). The discussion also highlighted that individuals differed in the value they placed on different side effects and expected benefits from the intervention. It was again described how patients were often willing to tolerate significant side effects and toxicity for seemingly minimal or modest survival benefits. Most acute side effects are self limited and reversible. Furthermore, they are largely preventable (nausea, vomiting, mucositis, and infectious complications). Emphasis was, therefore, placed on long-term, persistent, or life-threatening toxicities (premature menopause, osteoporosis, myelodysplastic syndromes, leukemias, second primary cancers, cardiac toxicity, and thromboembolic events) and the open discussion of both relative and absolute benefits from treatment for optimal treatment choices by individual patients. A variety of information and decision-making aids was discussed, although it was emphasized that none were a substitute for an open, empathetic discussion with a knowledgeable and empathetic health care provider.

Promising New Areas of Research in Adjuvant Therapy

Prospective randomized trials have provided the most compelling evidence about the adjuvant treatments discussed in this conference. Therefore, the importance of large, sufficiently powered, randomized trials was again endorsed. It was pointed out that only ~3% of cancer patients participate in clinical trials in the United States; this is in contrast with 30–50% in some European countries. Recent studies suggested that one of the important reasons why patients do not participate in trials is because their physicians do not offer or recommend participation. The efforts by the National Cancer Institute to make clinical trials more readily available to practicing physicians, and enhance clinical trial participation, resulting in more rapid translation of research results to the clinic. Important questions in the area of hormonal therapy included the continued evaluation of combined chemotherapy and ovarian ablation in well-selected patients with hormone receptor-positive tumors, the evaluation of the role of selective aromatase inhibitors and new selective estrogen receptor modulators in adjuvant therapy, and the assessment of combination hormonal therapies (e.g., tamoxifen with luteinizing hormone releasing hormone agonists or tamoxifen with aromatase inhibitors). The optimal duration of therapy with tamoxifen and other hormonal agents continues to be an important area of clinical research.

New research in adjuvant chemotherapy should include completion of the evaluation of the role of dose, dose density and dose intensity, the role of the taxanes, and other exciting new agents (vinorelbine, gemcitabine, and others).

Novel strategies must be tested prospectively; thus, the role of the anti-HER-2 monoclonal antibody (trastuzumab) and the bisphosphonates (pamidronate, clodronate, and zoledronic acid) is currently under investigation. Additional biological agents, including inhibitors of angiogenesis, matrix metalloproteinases, and tyrosine kinase inhibitors, will soon follow suit.

Methods to target therapies to groups of patients selected on the basis of more effective prognostic and predictive factors and testing adjuvant strategies in patients >70 years of age (a very large subset of patients with breast cancer) are of high priority in the research agenda.

The results of 4 decades of intensive investigation confirm the importance of multidisciplinary management of primary breast cancer. A policy of optimal locoregional therapy, combined with an anthracycline-containing chemotherapy regimen, and hormone therapy targeted to patients with hormone receptor-positive tumors should result in a 40–60% reduction in risk of recurrence and a 40–50% reduction in mortality, when compared to surgical therapy alone. The inclusion of taxanes, newer hormonal therapies, bisphosphonates, and other biologically based interventions is expected to further improve the prognosis of patients with breast cancer. Clinical research in this area should continue based on sound biological principles, optimal trial methodology, and enhanced participation by physicians and patients alike. Our markedly expanded understanding of the biology of breast cancer, the development of novel targets, and corresponding therapeutic agents provides us with enhanced opportunities for improved results. We hope the next Consensus Development Conference will find more progress than controversy to discuss.

References


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*Clin Cancer Res* 2001;7:1839-1842.

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