DRAFT STATEMENT
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NATIONAL INSTITUTES OF HEALTH
CONSENSUS DEVELOPMENT CONFERENCE STATEMENT
Adjuvant Therapy for Breast Cancer
November 1–3, 2000

NIH Consensus Statements are prepared by a nonadvocate, non-Federal panel of experts, based on (1) presentations by investigators working in areas relevant to the consensus questions during a 2-day public session; (2) questions and statements from conference attendees during open discussion periods that are part of the public session; and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

Introduction

Each year, more than 180,000 women in the United States are diagnosed with breast cancer, the most common type of noncutaneous cancer among women in this country. If current breast cancer rates remain constant, a woman born today has a one in ten chance of developing breast cancer.

Because of continuing research into new treatment methods, women with breast cancer now have more treatment options and a better chance of long-term survival than ever before. The primary treatment of localized breast cancer is either breast-conserving surgery and radiation or mastectomy with or without breast reconstruction. Systemic adjuvant therapies that are designed to eradicate microscopic deposits of cancer cells that may have spread or metastasized from the primary breast cancer have been demonstrated to increase a woman's chance of long-term survival.

Systemic adjuvant therapies include chemotherapy (anticancer drugs) and hormone therapy. In addition to these systemic therapies, radiotherapy is used in selected cases as a local adjuvant treatment to destroy breast cancer cells that remain in the chest wall or regional lymph nodes after mastectomy.

The rapid pace of discovery in this area continues to expand the knowledge base from which informed treatment decisions can be made. The purpose of this conference was to establish a consensus regarding the use of adjuvant therapy for breast cancer and to communicate that consensus to clinicians, patients, and the general public. After reading relevant literature and attending a day and a half of presentations and audience discussion, an independent, non-Federal consensus development panel weighed the scientific evidence and drafted a statement that was presented to the conference audience on the third day. The consensus development panel's statement addresses the following key questions:

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

This conference was sponsored by the National Cancer Institute and the NIH Office of Medical Applications of Research. The co-sponsors included the National Institute of Nursing Research and the NIH Office of Research on Women's Health.

1. Which factors should be used to select systemic adjuvant therapy?

The selection of systemic adjuvant therapy is based on prognostic and predictive factors. Prognostic factors are measurements available at diagnosis or time of surgery that, in the absence of adjuvant therapy, are associated with recurrence rate, death rate, or other clinical outcome. Predictive factors are measurements associated with degree of response to a specific therapy. For example, a demonstration of hormone receptors in tumor cells predicts the response to hormonal therapy. Any factor has the potential to be both prognostic and predictive, and a factor's importance depends on both the clinical endpoint and on the method of treatment comparison.

Prognostic and predictive factors fall into three categories: patient characteristics that are independent of the disease (such as age); disease characteristics (such as tumor size and histologic type); and biomarkers (measurable parameters in tissues, cells, or fluids), such as hormone receptor status, progesterone receptor status, and measures of cell turnover. Accepted prognostic and predictive factors include age, tumor size, axillary node status, histological tumor type, standardized pathologic grade, and hormonal-receptor status.

The median age for the diagnosis of breast cancer is between the ages of 60 and 65 years. Some younger women (particularly under 35 years) have a more agressive form of the disease, characterized by larger tumors of higher grade with vascular invasion. Elderly women (over 70 years) with breast cancer frequently have hormone receptor protein in their malignant tissue, suggesting a more indolent tumor pattern and a high likelihood of response to hormonal therapy.

Race appears to be a prognostic but not predictive factor. In contrast to white women, black breast cancer patients are generally younger, often have larger tumors at diagnosis, and a smaller percentage have hormone receptors in their tumor tissue. These factors contribute to a poorer prognosis. In cases of similar clinical presentation, however, adjuvant treatment confers

similar benefits to black and white women. Research on the benefits and risks of adjuvant therapy in Hispanic, Asian, and Native American women is needed.

Novel technologies (such as tissue and expression microarrays and proteomics) present exciting potential, but their integration into clinical practice will depend on the proper design and analysis of clinical investigations. The same is true for overexpression of HER-2/neu, p53 status, histologic evidence of vascular invasion, and quantitative parameters of angiogenesis. These have been extensively studied clinically and biologically, but do not have an established role in patient management. For example, although overexpression/amplification of HER-2/neu is associated with an adverse outcome in node-positive patients and may predict the response to therapy, laboratory methods and the reporting of results require standardization before its predictive performance can be established.

The development of immunohistochemical and molecular methods to identify occult cancer cells (i.e., micrometastases) in histologically tumor-free axillary lymph nodes or bone marrow has raised questions as to whether such findings should alter the clinical stage and become a further indication for systemic adjuvant therapy. At present, the clinical significance of these findings remains uncertain, and they require assessment in prospective clinical trials before they directly alter patient management.

It is essential that the value of predictive and prognostic factors be evaluated in well-designed clinical studies that are based on standardized protocols and have sufficient statistical power. Because these standards are infrequently met, very few new prognostic or predictive factors have been validated in the last 10 years, and future progress will depend on greater attention to these standards. Promising pilot studies should be followed by a validation phase, during which alternative assays for the biomarker are evaluated in a head-to-head comparison

and prognostic/predictive value is studied. Since no single study will have sufficient power to properly evaluate predictive value, results from these trials should be combined.

2. <u>For which patients should adjuvant hormonal therapy be recommended</u>?

The decision whether to recommend adjuvant hormonal therapy should be based on the presence of hormone receptors, as assessed by immunohistochemical staining of breast cancer tissue. If the available tissue is insufficient to determine hormone receptor status, it should be considered as being positive, particularly in postmenopausal women. The small subset of women whose tumors lack hormone receptor protein but contain progesterone receptor also appear to benefit from hormonal therapy. The presence or absence of HER-2/neu overexpression should not influence the decision to recommend hormonal therapy.

The goal of hormonal therapy is to prevent breast cancer cells from receiving stimulation from estrogen. Such stimulation occurs primarily in tumors that contain hormone receptor protein. Estrogen deprivation can be achieved by (a) blocking the receptor through the use of drugs, such as tamoxifen; (b) suppression of estrogen synthesis through the administration of aromatase inhibitors (e.g., anastrozole) in postmenopausal women or LHRH agonists (e.g., goserelin) in premenopausal women; or (c) destruction of the ovaries through surgery or external beam radiation therapy. The administration of cytotoxic chemotherapy may indirectly accomplish this same effect by damaging estrogen-producing cells in the ovaries.

Adjuvant hormonal therapy should be recommended to women whose breast tumors contain hormone receptor protein, regardless of age, menopausal status, involvement of axillary lymph nodes, or tumor size. While the likelihood of benefit correlates with the amount of hormone receptor protein in tumor cells, patients with any extent of hormone receptor in their tumor cells may still benefit from hormonal therapy. Such treatment has led to substantial

reductions in the likelihood of tumor recurrence, second primary breast cancer, and death persisting for at least 15 years of followup. Possible exceptions to this recommendation include premenopausal women with tumors less than 10 mm in size who wish to avoid the symptoms of estrogen deprivation or elderly women with similarly sized cancers who have a history of venous thromboembolic episodes.

Tamoxifen is the most commonly used form of hormonal therapy. Randomized trials and a meta-analysis have shown that 5 years of tamoxifen are superior to 1 to 2 years of such treatment. Currently, there are no convincing data that justify the use of tamoxifen for longer than 5 years outside the setting of a clinical trial. Although tamoxifen has been associated with a slight but definite increased risk of endometrial cancer and venous thromboembolism, the benefit of tamoxifen treatment far outweighs its risks in the majority of women. Neither transvaginal ultrasonography nor endometrial biopsies are indicated as screening maneuvers for endometrial cancer in asymptomatic women taking tamoxifen. Tamoxifen may be combined with combination chemotherapy, particularly in premenopausal women; such combinations may further reduce the risk of recurrence. There are no data to support the use of raloxifene or aromatase inhibitors as adjuvant hormonal therapy at this time.

For hormone receptor positive premenopausal patients, alternative strategies of hormonal therapy, which are used far less frequently in the United States, include ovarian ablation through surgery, radiation therapy to the ovaries, or chemical suppression of ovarian function. Ovarian ablation appears to produce a similar benefit to some chemotherapy regimens. Combining ovarian ablation with chemotherapy has not been shown to provide an additional advantage to date. The value of combining hormonal therapies has not yet been adequately explored.

Hormonal adjuvant therapy should not be recommended to women whose breast cancers do not express hormone receptor protein. Randomized clinical trials have not yet shown that such treatment substantially reduces the likelihood of recurrence or, in the case of tamoxifen, diminishes the likelihood of contralateral breast cancer.

3. For which patients should adjuvant chemotherapy be recommended? Which agents should be used, and at what dose or schedule?

Over the past decade, data have emerged that more clearly define the subpopulations of women with localized breast cancer for whom adjuvant chemotherapy is indicated as a standard component of treatment. Chemotherapy has been shown to substantially improve the long-term, relapse-free, and overall survival in both premenopausal and postmenopausal women up to age 70 years with node-positive and node-negative disease.

Randomized clinical trials have attempted to define optimal chemotherapy regimens, doses, and schedules in the adjuvant treatment of breast cancer. These studies, along with the results of overview analyses, permit a number of conclusions to be drawn.

The administration of polychemotherapy ($\geq$ 2 agents) is superior to single agents. Four to six courses of treatment (3 to 6 months) appear to provide optimal benefit, with the administration of additional courses adding to toxicity without substantially improving overall outcome. However, definitive data on the benefits of more prolonged treatment are lacking and future research is needed to directly address this clinically relevant issue.

Anthracyclines (such as doxorubicin and epirubicin) have been used as components of adjuvant polychemotherapy for breast cancer. Available data indicate that adjuvant chemotherapy regimens that include an anthracycline result in a small but statistically significant improvement in survival compared to nonanthracycline-containing programs. There is no evidence for

excessive cardiac toxicity in women without significant preexisting heart disease treated with anthracyclines at the cumulative doses utilized in standard adjuvant programs. In clinical practice, the decision to use an anthracycline in an individual patient should take into consideration the potential survival benefits versus specific concern about additional toxicity.

Randomized trials have demonstrated threshold dose effects for two of the most active chemotherapeutic agents, doxorubicin (A) and cyclophosphamide (C). These two drugs are frequently administered together (AC) and appear to result in a comparable survival outcome, whether given preoperatively or postoperatively. However, AC has not been compared to cyclophosphamide/doxorubicin/5-fluorouracil (CAF) or cyclophosphamide/epirubicin/5-fluorouracil (CEF). There is a need for future studies to address the issue of defining the optimal use of anthracycline-based therapy.

There is currently no convincing evidence to demonstrate that more dose-intensive treatment regimens (e.g., high-dose chemotherapy with peripheral stem cell support) result in improved outcomes compared to the administration of polychemotherapy programs at standard dose levels. Such stem cell-support treatment strategies should not be offered outside the setting of a randomized clinical trial.

Taxanes (docetaxel, paclitaxel) have recently been demonstrated to be among the most active agents in the treatment of metastatic breast cancer. As a result, several studies have explored the clinical utility of adding these drugs to standard doxorubicin/cyclophosphamide treatment programs in the adjuvant treatment of node-positive, localized breast cancer. Although a number of such trials have completed accrual and others remain in progress, currently available data are inconclusive and do not permit definitive recommendations regarding the impact of

taxanes on either relapse-free or overall survival. There is no evidence to support the use of taxanes in node-negative breast cancer outside the setting of a clinical trial.

Available data demonstrate that chemotherapy and tamoxifen are additive in their impact on survival when employed as adjuvant treatment of breast cancer. Therefore, most patients with hormone receptor positive tumors who are receiving chemotherapy should receive tamoxifen.

At the present time, there are no convincing data to support the use of any known biological factor in selecting a specific adjuvant chemotherapy regimen in breast cancer. Future prospective studies are needed to determine if such factors in an individual patient (e.g., HER-2/neu overexpression) should influence the choice of adjuvant cytotoxic therapy.

Despite the favorable impact of adjuvant chemotherapy on long-term survival in breast cancer, it is important to determine whether there are specific patient populations for whom it is reasonable to avoid the administration of cytotoxic chemotherapy. Unfortunately, very limited information is available to answer this important question. On the basis of available data, it is accepted practice to offer cytotoxic chemotherapy to most women with primary breast cancers larger than 1 cm in diameter (both node-negative and node-positive). For women with node-negative cancers less than 1 cm in diameter, the decision to consider chemotherapy should be individualized.

Similarly, in patients with small, node-negative breast cancers with favorable histologic subtypes, such as tubular and mucinous cancers, retrospective data support long-term survival following primary therapy without the need for adjuvant chemotherapy.

There are limited data to define the optimal use of adjuvant chemotherapy for women more than 70 years of age. It is likely that there is a survival benefit associated with the administration of chemotherapy in this patient population. There is legitimate concern, however,

regarding the toxicity associated with cytotoxic regimens in this population. In addition, existing comorbid medical conditions and mortality from noncancer causes will influence the overall benefits in this group of women. The decision to treat women over the age of 70 with adjuvant chemotherapy will need to consider these factors. Increased participation of women over 70 in randomized clinical trials and studies specifically addressing the value and tolerance of adjuvant chemotherapy in these women are urgently needed.

4. <u>For which patients should post-mastectomy radiotherapy be recommended</u>?

The standard of care for breast conservation includes surgery followed by breast radiotherapy. Before the advent of effective adjuvant chemotherapy, post-mastectomy radiotherapy was commonly employed. Interest in this approach was revived after several studies identified patient subgroups with 20 to 40 percent rates of locoregional recurrence after mastectomy and chemotherapy. These subgroups, which included women with four or more positive lymph nodes or an advanced primary tumor (a tumor of 5 cm or greater or a tumor invading the skin or adjacent musculature), were thought most likely to benefit from a course of post-mastectomy radiotherapy.

Recent randomized controlled trials have demonstrated superior tumor control and overall survival rates with the addition of post-mastectomy radiotherapy. A recent meta-analysis of more than 22,000 women comparing adjuvant radiotherapy to no radiotherapy reported an improvement in locoregional tumor control rates from 70 percent to 90 percent. This resulted in a significant improvement in the overall survival rate and in the disease-specific survival rate after a followup time of 20 years. These findings lend support to the concept that improving locoregional tumor control rates in breast cancer can lead to an improvement in survival rates.

The potential benefits of post-mastectomy radiotherapy must be weighed against both the acute and long-term side effects of this therapy. The same meta-analysis documented an excess of non-breast cancer deaths, the majority of which were vascular in nature. These deaths were probably related to the high radiotherapy doses received by the heart and great vessels through the use of outdated radiotherapy techniques. Contemporary radiotherapy delivery employing image-based planning has substantially reduced the radiotherapy dose received by these structures. Although the duration of followup of women treated with modern techniques is more limited, the preliminary data show no apparent increase in vascular deaths. Post-mastectomy radiotherapy, however, is associated with an increased risk of arm edema.

There is evidence that women with a high risk of locoregional tumor recurrence after mastectomy will benefit from postoperative radiotherapy. This high-risk group includes women with four or more positive lymph nodes or an advanced primary tumor. Post-mastectomy radiotherapy must be coordinated with adjuvant multiagent chemotherapy and/or hormonal therapy. Radiotherapy should not be delivered concurrently with anthracycline chemotherapy and should be delivered within the first 6 months following mastectomy. In most circumstances, combined modality adjuvant therapy begins with several courses of chemotherapy. Radiotherapy, as part of such treatment programs, should be delivered with modern techniques designed to reduce the volume of heart and great vessels receiving radiotherapy. At this time, the role of post-mastectomy radiotherapy for women with one to three positive lymph nodes remains uncertain and are being examined in a randomized clinical trial.

5. How do side effects and quality-of-life issues factor into individual decision-making about adjuvant therapy?

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

Acute, Long-Term and Late Medical Effects of Adjuvant Therapy

Adjuvant Chemotherapy

Studies to date have documented a range of acute and late side effects of adjuvant chemotherapy that have the potential for significantly affecting patients' quality of life. Most acute side effects (e.g., nausea and vomiting, mucositis, hair loss, neutropenia) occur in varying degrees in the different chemotherapy regimens and resolve after treatment completion. This also seems to be true for psychological distress. Several randomized studies have found that the psychological distress patients experience is greater during more toxic adjuvant chemotherapy treatment, resolving soon after treatment completion. Similarly, 1 to 3 years after completing treatment, the distress levels of cancer survivors who had undergone any of the different adjuvant chemoendocrine therapies equal the levels of those who had received no further adjuvant therapy.

The simultaneous combination of chemotherapy plus tamoxifen is associated with an increased risk of thromboembolism when compared to tamoxifen alone. Premature menopause, weight gain, and fatigue are the most frequent long- and short-term problems that have been

documented. Several small studies have documented mild cognitive problems, such as those in memory, with precise levels of prevalence and severity yet to be determined. There is also a very small increase in the risk of treatment-related second malignancies and cardiac disease.

Adjuvant Hormone Therapy: Tamoxifen and Ovarian Ablation

Hot flashes and vaginal discharge have been the most common side effects attributed to tamoxifen. Tamoxifen is associated with a small, increased risk of endometrial cancer, pulmonary emboli, deep vein thrombosis, particularly for those women 50 years old or older. The benefits, however, far outweigh the risks. Tamoxifen has not been associated with an increase in depression, weight gain, nausea and vomiting, diarrhea, or problems in sexual functioning.

As with adjuvant chemotherapy, ovarian ablation is associated with the development of premature menopause and its associated symptoms including osteoporosis.

Decision-making in Adjuvant Therapy for Breast Cancer

Communication between patients and their physicians is the primary vehicle through which complex treatment decisions are made. This communication will likely be facilitated through the use of decision aids, and well-designed patient information materials about the medical condition or procedure, treatment side effects, probabilities associated with health outcomes, and impact on quality of life. Findings from current research suggest that decision aids improve patients' knowledge about treatment options, reduce patients' anxiety about treatment decisions and enhance their comfort with treatment choices, and stimulate patients to play a more active role in joint decision-making with their physicians.

6. What are promising new research directions for adjuvant therapy?

During the past decade, major advances in adjuvant treatment of breast cancer have resulted from analyses of large prospective randomized trials. In the United States, however, fewer than 3 percent of cancer patients are entered in clinical trials. To achieve continued improvements in adjuvant treatment, efforts should be made to improve patient and physician participation in these studies. A number of important questions remain to be answered.

Randomized clinical trials should be conducted to better define the risks and benefits of continuing tamoxifen therapy beyond 5 years. Studies are also needed to expand experience with ovarian ablation, to explore the value of combined hormonal therapy, and to determine whether optimal hormonal therapy is equivalent, superior, or additive to chemotherapy in premenopausal women whose tumors express hormone receptor protein. The risks and benefits of new, selective estrogen receptor modulators (SERMs) and aromatase inhibitors should also be examined in the adjuvant setting.

Randomized clinical trials evaluating the roles of high dose chemotherapy and taxanes need to be completed to determine whether these treatments have a role in the standard management of breast cancer. Additional studies are also needed to determine the importance of variations in the doses and schedules of the drugs used in chemotherapy regimens that are currently accepted as being standard. A particular emphasis should be placed on carefully designed studies to determine the clinical and biological characteristics that may more accurately predict the effectiveness of specific adjuvant treatments in individual patients. As yet unproven treatments that must be critically evaluated in prospective trials in the adjuvant setting include trastuzumab, bisphosphonates, and newer chemotherapeutic and biologic agents.

To date, prospective trials of adjuvant therapy have failed to include sufficient numbers of women older than 70 years. Studies need to be designed that will determine the effectiveness of adjuvant therapies in this group of women.

The role of post-mastectomy radiotherapy in women with 1 to 3 positive lymph nodes needs to be determined. Investigators should continue to explore the importance of risk factors for recurrence after mastectomy to improve the selection of patients who may benefit from adjuvant radiotherapy. To maximize the possible benefit of adjuvant radiotherapy, new radiation techniques should be developed that further reduce the radiation dose to normal tissues, such as the heart and lungs.

Although adjuvant therapy has been found to produce significant improvements in survival, the ability to predict the value of these treatments in individual patients is limited. The development of accurate predictors of treatment efficacy would permit better targeting of treatments, improving efficacy and reducing the morbidity and cost of treatment. It is essential that the value of predictive and prognostic factors be evaluated using standardized protocols in well-designed clinical studies with sufficient statistical power to detect clinically important differences. Successful integration of new technologies, such as tissue and expression microarrays and proteomics, will depend on careful design and analysis of clinical investigations. The value of sentinel lymph node biopsy and of sensitive assays for micrometastatic disease in lymph nodes and bone marrow should also be important priorities for clinical research.

Quality-of-life and late-effect evaluations should be judiciously integrated into selected clinical trials to better discern the acute and long-term influence of treatment on patients and their families. Interventions should be sought that will reduce side effects and improve quality of life.

Decision aids and other techniques should be developed and evaluated for their ability to improve patients' involvement and understanding of treatment decisions.

Conclusions

During the past 10 years, substantial progress has been made in the treatment of breast cancer. For the first time, breast cancer mortality rates are decreasing in the United States. Refinements of adjuvant treatment have contributed to this advance.

Generally accepted prognostic and predictive factors include age, tumor size, lymph node status, histological tumor type, grade, mitotic rate, and hormonal receptor status. Novel technologies, such as tissue and expression microarrays and proteomics, hold exciting potential. Progress, however, will depend on proper design and analysis of clinical and pathological investigations.

Decisions regarding adjuvant hormonal therapy should be based on the presence of hormone receptor protein in tumor tissues. Adjuvant hormonal therapy should be offered to women whose tumors express hormone receptor protein. At present five years of tamoxifen is standard adjuvant hormone therapy; ovarian ablation represents an alternative option for selected premenopausal women. Adjuvant hormonal therapy should not be recommended to women whose tumors do not express hormone receptor protein.

Because adjuvant polychemotherapy improves survival, it should be recommended to the majority of women with localized breast cancer regardless of nodal, menopausal, or hormone receptor status. The inclusion of anthracyclines in adjuvant chemotherapy regimens produces a small but statistically significant improvement in survival over nonanthracycline-containing regimens.

Available data are currently inconclusive regarding the use of taxanes in adjuvant treatment of node-positive breast cancer. The use of adjuvant dose-intensive chemotherapy regimens in high-risk breast cancer and of taxanes in node-negative breast cancer should be restricted to randomized trials. Ongoing studies evaluating these treatment strategies should be supported to determine if they have a role in adjuvant treatment.

Studies to date have included few patients older than 70 years. There is a critical need for trials to evaluate the role of adjuvant chemotherapy in these women.

There is evidence that women with a high risk of locoregional tumor recurrence after mastectomy benefit from postoperative radiotherapy. This high-risk group includes women with four or more positive lymph nodes or an advanced primary cancer. Currently, the role of post-mastectomy radiotherapy for patients with one to three positive lymph nodes remains uncertain and should be tested in a randomized controlled trial.

Individual patients differ in the importance they place on the risks and benefits of adjuvant treatments. Quality-of-life needs to be evaluated in selected randomized clinical trials to examine the impact of the major acute and long-term side effects of adjuvant treatments, particularly premature menopause, weight gain, mild memory loss, and fatigue. Methods to support shared decision-making between patients and their physicians have been successful in trials; they need to be tailored for diverse populations and should be tested for broader dissemination.

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