COMMENTARY

Meeting Highlights: International Consensus Panel on the Treatment of Primary Breast Cancer

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Providing effective care for patients with early stage breast cancer and designing appropriate recommendations for women at high risk of developing the disease are important public health goals. More than ever, progress requires integrated understanding based on the continuous interaction among several scientific and clinical disciplines. In February 1998, the 6th International Conference on Adjuvant Therapy of Primary Breast Cancer was held in St. Gallen, Switzerland. Knowledge of breast cancer genetics, diagnosis, and treatment has evolved since the 5th International Conference that was held in March 1995. At that time, a fundamental theme was to distinguish the role of prognostic factors used in the definition of risk from predictive factors used for the selection of adjuvant treatments according to therapeutic responsiveness *(1).* Also at that time, the findings from the 1992 Overview publication *(2)* that reported results on ovarian ablation, tamoxifen, and chemotherapy effects were being increasingly applied to justify adjuvant treatment for a wider spectrum of indications.

Since 1995, several specific areas have accumulated important new information and were highlighted at this year's conference. These include the following: genetic testing of women at risk; the availability of chemopreventive agents for high-risk and postmenopausal women; changes in diagnostic procedures with an intent to reduce axillary dissection by introducing sentinel-node biopsy; results from trials of preoperative chemotherapy; initiatives to evaluate preoperative endocrine therapies; and debates on the role of increased local control by postmastectomy radiation therapy, its safety, and its effectiveness.

At the conclusion of the conference, a consensus panel of experts was asked—as at the previous conference *(1)*—to develop a series of guidelines and recommendations for selection of adjuvant systemic treatments in specific patient populations. The panel reviewed and modified its previous guidelines and recommendations based on new evidence that has emerged from clinical research.

During the past 3 years, several new fields of interest have emerged and a variety of treatment strategies have been tested. Some of these strategies can be added to the repertoire of treatments available for patients today, while others are still undergoing clinical investigation for a better assessment of their potential usefulness in the future. Table 1 describes some examples of these recent findings and their implications for or status relative to patient care. In this commentary we describe some areas of ongoing research and update the adjuvant treatment recommendations presented 3 years ago.

Prognosis and Prediction of Response

Several factors have been identified that define those patients who should not receive any form of adjuvant systemic therapy. The panel agreed that a population of patients who have less than a 10% chance of relapse within 10 years would not be candidates for receiving routine adjuvant systemic therapy. This represents a change from the conclusions of the previous panel, which recommended that such exclusion be based on a 10-year *mortality* of 10% or less. The modification reflects the panel's consensus that patient's preference to avoid relapse might be used for consideration of adjuvant chemotherapy, even when the risk of death from breast cancer is quite low. Data from cohorts followed for less than 10 years were felt to be insufficient to define a group at minimal risk.

The most relevant factors for the estimation of risk remain the nodal status and the number of nodes involved. For patients with node-negative disease, tumor size, histologic and nuclear grade, steroid hormone receptor status, lymphatic and/or vascular invasion, and age are factors considered by the panel to define groups with differential prognosis for use in treatment selection (Table 2). Additional considerations about a low relative risk of relapse within a risk category, toxic effects, socioeconomic implications, and information on patient's preference might also contribute to treatment decision making.

Two new strategies were discussed as having great potential for altering the estimation of risk; both require validation by future studies before they are ready for routine use outside of clinical research. First, staging of the axilla might change if sentinel lymph node biopsy and work-up, a limited staging procedure, replaces complete axillary dissection as the source of information on axillary nodes *(6).* Second, the use of preoperative systemic therapy will influence the prognostic information available. The assessment of pathologic features of the primary tumor will have to rely on limited material obtained from a core

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See ''Appendix'' for list of other panel members.

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See ''Notes'' following ''References.''

Table 1. Recent research findings presented at the 6th International Conference on Adjuvant Therapy of Primary Breast Cancer and their implications for patient care

Field or treatment	Status of research/implications for patient care
Epidemiology	Recognition of risk factors (markers of risk that cannot be changed; e.g., sex, age, or height) and risk determinants (factors that, if changed, would alter the frequency or characteristics of the disease; e.g., exposure to ionizing irradiation, estrogen-replacement therapy, alcohol consumption, body mass, and perhaps diet).
Genetics	The availability of testing for mutations in the BRCA1 and BRCA2 genes has led to the definition of new subpopulations of women with a substantially increased risk of developing breast (and ovarian) cancer. The lack of effective preventive modalities for these women complicates recommendations for testing and follow-up *(3)*. Screening to define individual risk is thus not ready for routine use and presents challenges for the management of major personal, ethical, and therapeutic dilemmas. Ongoing and future chemoprevention trials might have an important impact upon the use of genetic information.
Chemoprevention	Trials to test tamoxifen as a chemopreventive agent (motivated by a 40% reduction in the risk of contralateral breast cancer observed in randomized adjuvant therapy trials) have accrued about 20 000 women. [After the conference, on April 5th, National Surgical Adjuvant Breast and Bowel Project (NSABP) released the first results for 13 388 women in the NSABP Breast Cancer Prevention Trial which showed, after about 4 years' median follow-up, a similar reduction in invasive cancer and ductal carcinoma *in situ* (DCIS) in the tamoxifen-treated group. This study has recently been published *(46)*]. Another antiestrogen, raloxifene, tested for reduction of osteoporosis *(4)*, was shown after a short treatment and follow-up duration to reduce breast cancer incidence in women more than 60 years of age. Fenretinide (4-HPR), a retinoid tested in patients with node-negative disease, showed some effect on reducing the incidence of contralateral breast cancer in premenopausal women.
Treatment of DCIS	Incidence of DCIS has increased substantially in recent years as a result of refined and intensified diagnostic procedures, mainly mammography. Although the spread of tumor cells in these lesions is intraductal, the principles guiding the surgical management of these lesions are the same as those for invasive cancer—localization and total removal of the primary tumor with clear resection margins. Conservation of the breast, if possible and desired, should be attempted. If there is no invasive component, no additional prognostic information is obtained by removal of the axillary lymph nodes. Therefore, axillary dissection is not indicated. Radiation therapy to the conserved breast after a complete surgical removal of a DCIS lesion showed a statistically significant relative reduction (fourfold) in subsequent invasive tumor growth in the breast *(5)*. This issue is still under investigation in Europe. Additional research is directed toward determining whether tamoxifen is effective in preventing relapse and invasion following treatment of DCIS.
Extent of surgery to the breast and to the axilla	Breast conserving surgery (and planned radiation therapy to the conserved breast) is the treatment of choice for unifocal, invasive breast cancer that can be excised with clear margins. The importance of clear margins (defined as normal tissue of about 1 cm surrounding the tumor) has been demonstrated, although clear margins do not guarantee freedom from local recurrence. Axillary staging through the pathologic evaluation of the first lymph node that drains the tumor area (sentinel node biopsy) was tested to avoid extensive surgery on a negative axilla *(6)*. The proper technique to use, extent of the pathology work-up, and training required for an accurate and reproducible result have yet to be determined; thus, the method remains investigational. While axillary dissection is considered the proper staging procedure for breast cancer, its impact on curability of the disease is unclear, especially in patients with clinically N0 disease who are given adjuvant therapy.
Biologic therapies, immunotoxins, antibodies, and gene therapy	Treatments with monoclonal antibodies, especially in combination with cytotoxic drugs, still await demonstration of relevant clinical effect. Vaccines against breast cancer cell components are being tested *(7)*. Modulation of growth factors (e.g., insulin-like growth factor 1) *(8)* and inhibition of angiogenesis *(9)* are being evaluated in the clinical setting.
Factors for prediction of treatment responsiveness	The steroid-hormone receptor status of the primary tumor is the only marker of treatment response that has unequivocal clinical utility. There is some uncertainty about the level of receptor expression to use as the threshold for responsiveness to endocrine therapies. Standardization of the assay procedure is desirable. Measurement of C-erbB2 expression for prediction of response to anthracycline-containing chemotherapy and for resistance to treatment with tamoxifen or CMF requires further prospective verification because currently available information is exclusively from retrospective studies *(10)*.
Preoperative (primary) systemic therapy	Preoperative chemotherapy has been shown to be safe, yielding similar results in terms of disease-free survival and overall survival as did the same regimen when used following surgery. Patients who received preoperative chemotherapy were more likely to become eligible for breast conservation *(11)*. Clinical and pathologic response to primary chemotherapy was associated with prolonged disease-free survival. Primary endocrine therapy with new aromatase inhibitors or pure antiestrogens is being investigated; however, primary treatment with tamoxifen appears less effective than surgery followed by tamoxifen in terms of control of disease.
Radiation therapy after mastectomy	Breast irradiation is clearly indicated after breast conserving surgery. Recent trials in postmastectomy patients *(12,13)* indicated that some patients at very high risk of local recurrence might benefit, even with increased survival, from local and regional postoperative radiation therapy (50-Gy comprehensive treatment, appropriately planned and delivered). Controversies exist, however, concerning the adequacy of surgery and systemic treatment delivered in these trials *(14)*. Nevertheless, the approximately fourfold decrease in the risk of local-regional recurrence is likely to provide a non-negligible benefit in terms of systemic disease control and survival for patients at high risk of such recurrence. Postmastectomy radiation is thus to be considered for patients who, despite proper surgery and adjuvant systemic therapy, are at high risk of local recurrence (a risk of 20% or more; e.g., those presenting with four or more metastatic axillary lymph nodes). The components of the radiation plan (chest wall, internal mammary nodes, and axilla) were not separately investigated and are under investigation in clinical trials. The safety of local and regional radiation therapy given following anthracycline and/or taxane therapy has not been elucidated.
High-dose chemotherapy and taxanes	High-dose chemotherapy in the adjuvant setting, that uses a fourfold to 10-fold increase in dose with autologous bone marrow or peripheral blood progenitor cell support (with the aid of hematopoietic growth factors), is a promising approach for patients at high risk of relapse but remains investigational *(15)*, since definitive results from clinical trials are not yet available. Also, the use of taxanes in the adjuvant setting—either in concurrent or sequential combination with other cytotoxic drugs—is under intensive investigation.

Table 2. Risk categories for patients with node-negative breast cancer

Factors*	Minimal/low risk (has all listed factors)	Intermediate risk (risk classified between the other two categories)	High risk (has at least one listed factor)
Tumor size†	≤1 cm	>1–2 cm	>2 cm
Estrogen receptor (ER) and/or progesterone receptor (PgR) status‡	Positive	Positive	Negative
Grade§	Grade 1 (uncertain relevance for tumors ≤1 cm)	Grade 1–2	Grade 2–3
Age, y‖	≥35		<35

*Some panel members also recognize lymphatic and/or vascular invasion as an important feature that indicates an increased risk.

†It was generally agreed by the panel members that pathologic tumor size (i.e., size of the invasive component) was the most important prognostic factor for defining the additional risk of relapse.

‡ER status and PgR status are important biologic characteristics that identify responsiveness to endocrine therapies.

§Histologic and/or nuclear grade.

‖Patients who develop breast cancer at a young age are considered to be at high risk of relapse, although an exact age threshold for this increased risk has not been defined.

biopsy. The characteristics of the primary tumor and axillary lymph nodes observed in samples obtained after preoperative systemic therapy may be modified from those that would have been observed following primary surgery alone. On the other hand, the use of primary systemic therapy contributes additional prognostic features, specifically the clinical and pathologic responses of the primary tumor to preoperative therapy *(11,16).*

Expression of steroid hormone receptors in tumor cells is the most relevant factor predicting treatment response to endocrine therapy (Table 1). However, the methods used to assess estrogen receptor and progesterone receptor status have changed rapidly in recent years. Cutoff points based on immunohistochemical assay results to define endocrine-therapy responsiveness are still being evaluated. This is especially true for tumors with no or a low percentage of cells that stain for steroid hormone receptors *(17).* In particular, the decision to avoid the use of endocrine therapies might require that no expression of such receptors be observed, whereas if 10% or more of the tumor cells are stained for these receptors, an unequivocal response to endocrine therapy is likely.

The accurate definition of node-negative status requires that proper surgical dissection (to levels I and II) be performed and a sufficient number of axillary lymph nodes be examined. For routine use, axillary staging should be based on a sufficient number of examined lymph nodes (usually at least 10) to obtain the proper prognostic information *(18).* Methods that investigate proliferative features of the primary tumor, its invasive, metastatic, and angiogenic potential, require prospective studies and assessment with respect to specific treatment programs.

Consensus Panel Recommendations and Guidelines

Table 3 summarizes the recommendations and guidelines for postoperative adjuvant systemic therapy for early breast cancer proposed by the International Consensus Panel during the St. Gallen Conference, 1998. The panel emphasized that these guidelines are based on evidence from clinical trials demonstrating that various adjuvant therapies can reduce the risk of relapse and increase survival duration. They are not intended to be used to define required treatment for all patients, since individual circumstances and attitudes toward treatment and resources may vary in different parts of the world.

The format used to construct Table 3 reflects the four issues that are considered during treatment decision making outside of the framework of clinical trials: prognosis, prediction of treatment response, extrapolation of results on treatment effects obtained from randomized trials, and consideration of patient's preference concerning risks and benefits of effective therapies.

Four patient populations have been defined, based on the risk for relapse (prognosis) as described by the columns in Table 3, A and B (node negative with minimal/low risk, with intermediate risk, or with high risk; node positive). The rows in Table 3 represent different treatment–response (or predictive) factors, including steroid hormone receptor status of the primary tumor and whether ovarian function suppression can be added as a therapeutic modality (premenopausal versus postmenopausal status). Also, elderly patients are listed separately, since specific considerations are required concerning trade-offs between burdens of treatment, risks of relapse, and competing causes of morbidity and mortality.

Within the body of Table 3, we distinguish between therapies for which direct evidence is available that have demonstrated treatment effects based on the results of randomized, controlled clinical trials (**bold text**) and those therapies that are still investigational (double dagger [‡]). Finally, footnotes to Table 3 indicate specific areas in which patient preference should be taken into consideration when defining appropriate treatment. Physicians should elicit the preferences of their patients concerning aversion to side effects and attitudes toward disease recurrence and weigh these preferences against the uncertainty of prognosis and of treatment effectiveness (i.e., uncertainty of the absolute magnitude of the benefit to be achieved). The recommendation to take patient preference into consideration in planning treatment does not mean that, when a physician is uncertain about what to do, he or she should invite the patient to decide. Rather, the panel emphasizes in the Table 3 footnotes that physician judgment based on patient preference is an acceptable way to select adjuvant treatment.

Table 3. Adjuvant treatment for patients with node-negative (A) and node-positive (B) breast cancer*

A. Node negative

Patient group	Minimal/low risk	Intermediate risk	High risk
Premenopausal, ER or PgR positive	**None or tamoxifen**	**Tamoxifen ± chemotherapy**† Ovarian ablation‡ GnRH analogue‡	**Chemotherapy + tamoxifen**† Ovarian ablation‡ GnRH analogue‡
Premenopausal, ER and PgR negative	Not applicable	Not applicable	**Chemotherapy**§
Postmenopausal, ER or PgR positive	**None or tamoxifen**	**Tamoxifen ± chemotherapy**†	**Tamoxifen + chemotherapy**†
Postmenopausal, ER and PgR negative	Not applicable	Not applicable	**Chemotherapy**§
Elderly	**None or tamoxifen**	**Tamoxifen** ± chemotherapy	**Tamoxifen** If no ER and PgR expression: **chemotherapy**

B. Node positive

Patient group	Treatments
Premenopausal, ER or PgR positive	**Chemotherapy + tamoxifen** **Ovarian ablation** (or GnRH analogue) ± tamoxifen‡ Chemotherapy ± ovarian ablation or (GnRH analogue) ± tamoxifen‡
Premenopausal, ER and PgR negative	**Chemotherapy**§
Postmenopausal, ER or PgR positive	**Tamoxifen + chemotherapy**†
Postmenopausal ER and PgR negative	**Chemotherapy**§
Elderly	**Tamoxifen** If no ER and PgR expression: **chemotherapy**

*ER = estrogen receptor; PgR = progesterone receptor; GnRH = gonadotropin releasing hormone. Bold entries are treatments accepted for routine use or baseline in clinical trials.

†The addition of chemotherapy is considered an acceptable option based on evidence from clinical trials. Considerations about a low relative risk of relapse, age, toxic effects, socioeconomic implications, and information on patient's preference might justify the use of **tamoxifen alone**.

‡Indicates treatments still being tested in randomized clinical trials.

§The addition of tamoxifen following chemotherapy might be considered for patients whose tumors are classified as ER and PgR negative but which exhibit minimal/trace levels of either ER or PgR.

NODE-NEGATIVE BREAST CANCER

Treatment for patients with node-negative disease varies substantially according to the prognosis, based on patient and tumor characteristics. For patients considered at high risk of recurrence, the treatment choice follows an algorithm similar to that for node-positive disease, which has a similar prognosis. For high-risk patients, the use of chemotherapy alone was considered to be appropriate when steroid hormone receptors are absent in the primary tumor. For patients with tumors that express estrogen or progesterone receptors, combined chemotherapy and tamoxifen was shown in a clinical trial *(19)* to be more effective than endocrine therapy alone, irrespective of menopausal status. This trial tested, in combination with tamoxifen, the ''classical'' CMF-based regimen with oral cyclophosphamide on days 1–14 and intravenous methotrexate and 5-fluorouracil on days 1 and 8, repeated every 28 days. The use of anthracyclines for these patients is currently undergoing investigation and it is anticipated that their use might result in a small, but statistically significant, improvement in treatment outcome.

For patients with minimal/low-risk disease, the question of whether or not to treat with tamoxifen depends on a risk–benefit analysis, which should take into account both the low relapse rate within the first 10 years in these patients and the potential reduction by tamoxifen of the incidence of contralateral breast cancer. Patients classified as intermediate risk may be assigned to receive the same chemoendocrine treatment as the high-risk group, although considerations about a lower relative risk of relapse, age, toxicity, socioeconomic implications, and information on patient's preference might justify the use of tamoxifen alone as an endocrine treatment (e.g., a 65-year-old patient with a tumor expressing estrogen and progesterone receptors might be offered treatment with tamoxifen alone). For premenopausal women in this category, the use of hormonal manipulations other than tamoxifen, including ovarian ablation (either surgical or with gonadotropin-releasing hormone [GnRH] analogues), remains investigational, especially considering long-term side effects of these treatments.

NODE-POSITIVE BREAST CANCER

Additional information became available since the last conference on the treatment of patients with node-positive presentation. For patients who had their tumors classified as estrogen or progesterone receptor-positive, tamoxifen and chemotherapy with an anthracycline-based regimen *(20,21)* or with the classical CMF regimen *(22)* were shown to yield a significant prolongation of disease-free survival as compared with tamoxifen alone. The use of tamoxifen alone in women of postmenopausal age may, however, be justified based on individual considerations related to risk of relapse, age, and assessment of the patient's preference *(23).* Investigations on the type of regimen to be used in patients with node-positive disease take into account the cytotoxic agents to be used, dose intensification, increased frequency of chemotherapy administration, and the use of taxanes in sequential and concomitant combination (mainly with anthracyclines). The use of anthracyclines is usually accepted as a standard, based on interpretation of clinical trial information *(24,25).* Recently published Overview data *(47)* indicate a very modest, albeit statistically significant, difference favoring

anthracycline-based regimens compared with CMF-like treatments. Treatment options for this population of patients are shown in Table 3, B.

Specific Aspects of Treatment

Preoperative Systemic Therapy

Starting the therapy for patients with breast cancer with a systemic treatment immediately after diagnosis represents a strategy aimed theoretically at influencing tumor growth, avoiding development of resistance, reducing the number of positive axillary lymph nodes and/or the size of the tumor (i.e., downstaging), and improving control of local and potentially also of systemic disease—thereby increasing the number of patients who are candidates for breast conservation *(11,16,26,27).* Similar results in terms of disease-free and overall survival were obtained in a randomized trial comparing the same systemic chemotherapy regimen given preoperatively or postoperatively *(26).* It is interesting to note that the histologic features that are assessed postoperatively, such as the extent of axillary lymph node involvement and—especially—the degree of response by the tumor to primary chemotherapy, were found to be the features with the most significant association with prognosis. Some current clinical research is directed toward increasing the efficacy of the preoperative treatment regimen to try to obtain more complete tumor regression. The regimens being tested as primary systemic treatment are typically those used as postoperative adjuvant therapies as well as regimens developed for locally advanced disease that include continuous infusion of 5-fluorouracil. The use of the latter agent has led to a relatively large number of complete pathologic remissions *(28,29).*

Surgical Treatment of the Axilla

It has become axiomatic that the histopathologic evaluation of the axilla is the most important tool for estimation of risk of relapse. It has also been observed that node-positive and some node-negative disease presentations currently tend to receive similar treatments, thus making the determination of nodal status potentially irrelevant for treatment selection. Furthermore, it is unclear whether patients with nonpalpable axillary lymph nodes but with microscopic evidence of metastatic involvement benefit from surgical removal of these lymph nodes. Finally, it is clear that patients found not to have axillary lymph node involvement have had their lymph nodes removed at a cost of subsequent discomfort in return for having received reassuring information about the absence of tumor spread to the lymph nodes. Two new lines of research may change clinicians' attitudes toward whether performing axillary dissection should be part of a proper work-up at diagnosis. One area of research is the use of primary systemic therapy (*see above*), which leads to some downstaging of axillary involvement, especially in tumors that are particularly responsive to treatment. The other is the study of the sentinel lymph node (Table 1). This procedure may be investigated most usefully in patients who present with a localized, unicentric breast tumor *(6).* In addition to whether use of the procedure is feasible and whether a negative histopathologic finding by this procedure has clinical relevance, one of the most important open questions about the procedure remains whether finding a positive sentinel node means that further axillary dissection is needed.

Radiation Therapy After Breast Conserving Surgery and Mastectomy

Women who undergo breast conservation should be advised to have postoperative breast irradiation, mainly because its omission increases the risk of in-breast recurrence. Some impediments to breast irradiation include previous radiotherapy to the breast (for other malignant disorders), pregnancy, and anatomic hindrance to properly conduct the treatment. Autoimmune disorders are relative contraindications. Local breast irradiation should be started as soon as possible after surgery, usually within 12 weeks, except for patients in whom radiotherapy is preceded by chemotherapy. Selected chemotherapy regimens are sometimes used concurrently with radiotherapy, although there is an increased chance of toxic effects, especially when patients are given anthracycline-containing regimens.

On the basis of two recently published trials, patients at increased risk for local-regional recurrence after mastectomy (defined as at least a 20% cumulative risk of local-regional recurrence in spite of proper surgery and proper adjuvant systemic therapy) are considered to be candidates for postmastectomy irradiation *(12,13)* (Table 1). The Danish Trial 82b *(12)* confirms the observation that 50-Gy comprehensive local-regional radiotherapy, appropriately planned and delivered, reduces the proportional risk of local-regional recurrence after total mastectomy and (partial) axillary dissection by a factor of about four. In this premenopausal patient population, the group that received radiation therapy in addition to a chemotherapy regimen had improved overall survival as compared with the group treated with the chemotherapy regimen alone. The British Columbia Trial *(13),* although small, showed similar results. The benefit and safety associated with the combination of radiation therapy and different chemotherapy regimens, especially anthracyclines (and taxanes), remain the subjects for investigation *(30).* The panel concluded that postmastectomy radiation therapy was clearly to be considered for patients with an increased risk of local-regional recurrence following adequate surgery and adjuvant systemic therapy.

Ovarian Ablation

The Overview results *(31)* indicated that ovarian ablation can have beneficial effects in women with primary breast cancer. This treatment significantly improved the long-term survival for women under 50 years old, at least in the absence of chemotherapy. The report called for further evidence from randomized clinical trials to define the additional effects of ovarian ablation in the presence of other adjuvant treatments, especially in relationship with hormone-receptor status. The occurrence and severity of long-term side effects are still significant issues when this treatment is given to younger women, especially because the safety of treatments for the resulting menopausal symptoms is unknown for this cohort of patients.

At least four randomized trials include a GnRH analogue to suppress ovarian function. In these trials, the duration of treatment varies from 2 to 5 years. The shorter-duration treatments are justified by data showing that the amenorrhea induced by

chemotherapy is associated with improved disease-free survival, even if the patients resume menses after a cessation of at least nine months *(32)*. In advanced disease, a direct comparison between surgical ovarian ablation and the use of a GnRH analogue (goserelin) resulted in similar failure-free and overall survival *(33)*. However, the routine use of GnRH analogues in the adjuvant setting must await results of clinical trials.

Tamoxifen

Tamoxifen continues to be an important component of adjuvant treatment for patients with tumors that express steroid hormone receptors. Recently published Overview results *(34)* show that, for women with estrogen receptor-positive tumors, the magnitude of the treatment effect of tamoxifen was similar for all age cohorts—even extending to the youngest patients. Many of the panelists noted that the magnitude of treatment effects for younger patients demonstrated in the tamoxifen overview was even larger than that shown in the chemotherapy overview without regard to estrogen receptor status. Unfortunately, these observations based on indirect evidence are being used to argue that tamoxifen rather than chemotherapy should be the treatment of choice for younger women. In fact, such an argument contradicts the results of randomized trials that directly compare tamoxifen (for 2 years only) versus chemotherapy in young patients *(35)*. It is likely that 5 years of tamoxifen would have yielded a larger effect, thus providing the proper test to identify the best available among the single modalities of adjuvant systemic treatments. It should be stressed that the tamoxifen overview results excluded patients with estrogen receptor-poor tumors and thus was restricted to an endocrine treatment-responsive population. In addition, several issues with respect to the use of this compound still need answers from clinical trials. Although evidence exists that tamoxifen treatment of 5 years' duration yielded an improved disease-free survival as compared with a 2-year duration *(36)*, the evidence from trials of longer tamoxifen exposure is not entirely conclusive *(37)*, especially for patients with node-positive disease. For patients with node-negative breast cancer, 5 years is the standard duration of tamoxifen treatment. Also, the optimal way to administer the drug—either concomitant with or sequential to chemotherapy—is still unsettled, and a trial that was specifically designed to answer this question is still awaiting evaluation of this specific comparison *(21)*.

Chemotherapy Regimen and Dose

Anthracycline-based regimens have been increasingly introduced into clinical practice, primarily motivated by the shorter duration of treatment that they permit. This was based on the large National Surgical Adjuvant Breast and Bowel Project (NSABP) trial, in which four courses of doxorubicin and cyclophosphamide given every 3 weeks provided similar results compared with six courses of cyclophosphamide, methotrexate, and 5-fluorouracil (classical CMF) repeated every 4 weeks *(38)*. Recently published Overview data *(47)* on all trials begun before 1990 that compared anthracycline-containing regimens with CMF-like regimens indicate a very modest, although statistically significant, difference in favor of anthracycline use. Individual studies have shown a more toxic anthracycline-containing combination to be superior to a less toxic CMF. Such a regimen was used in the Canadian trial of cyclophosphamide, 4-epidoxorubicin, and 5-fluorouracil (CEF) given on a CMF-like schedule (4-epidoxorubicin and 5-fluorouracil given on days 1 and 8 every 4 weeks and cyclophosphamide given orally on days 1–14). To successfully reduce the incidence of febrile neutropenia *(25)*, this regimen was given together with antibiotics. Another anthracycline-based regimen that used a low-dose doxorubicin on day 1 but a daily 5-fluorouracil administration on days 3–6 each 28-day course was found to yield a disease-free survival advantage when compared with CMF in a small, randomized trial *(39)*. These observations indicate that a more toxic anthracycline regimen might represent the most effective ''conventional'' adjuvant regimen.

Many trials of adjuvant therapy used altered forms of CMF, although no trial directly compares classical and ''altered'' CMF in the adjuvant setting. However, several randomized trials have shown that departure from the classical CMF regimen compromises its efficacy for patients with metastatic breast cancer *(14)*. Further indirect evidence of the inferiority of altered CMF regimens comes from the seven adjuvant therapy trials that have compared CMF regimens plus tamoxifen with tamoxifen alone. A benefit of adding CMF was seen in all three trials that used classical CMF but in none of the four trials using CMF schedules given on day 1 every 3 or 4 weeks or at a low continuous dosage *(40)*.

Chemoendocrine Therapies

Combined chemotherapy and tamoxifen was associated with a better therapeutic outcome when compared with tamoxifen alone in all trials investigating this comparison, especially if the tested cytotoxic regimens contained anthracyclines (such as doxorubicin with or without cyclophosphamide or 4-epidoxorubicin) *(20,21,38)*. Trials that used CMF-like regimens in combination with tamoxifen showed a benefit in terms of disease-free survival only when the chemotherapy regimen used was ''classical'' CMF *(19,22);* no advantage in favor of the chemoendocrine therapy was detected when ''altered'' CMF regimens were used *(41–44)*. Evidence of an interaction between the effects of tamoxifen and chemotherapy is available both from laboratory *(45)* and from clinical *(22)* studies.

High-Dose Chemotherapy With Peripheral Blood Progenitor Cell or Bone Marrow Support

This procedure continues to be experimental because evidence from reliable, large-scale clinical trials is not yet available to indicate a more favorable treatment outcome for patients treated with high-dose chemotherapy *(15)*, either for patients with 10 or more metastatic axillary lymph nodes or with advanced disease.

Panelists' Additional Comments

The international panel attempted to answer many questions related to the best use of treatments investigated in randomized clinical trials. The panel members were more convinced than ever that participation in clinical trials must become more acceptable to the public as well as to the medical community for much more to be achieved that increases knowledge about the

disease and improves patient care. The members of the panel expressed their concern that excessive extrapolation of results from existing clinical trials and reliance upon indirect evidence might be detrimental to the development and validation of effective treatments.

APPENDIX

The other members of the panel are listed below. All had a significant input to the discussion and the manuscript: J. S. Abrams, National Cancer Institute, Bethesda, MD; M. Baum, University College-London, U.K.; F. Boccardo, National Institute for Cancer Research, Genoa, Italy; A. S. Coates, Australian Cancer Society, Sydney, Australia; B. Fisher, University of Pittsburgh, PA; A. Howell, Christie Hospital, Manchester, U.K.; M. Kaufmann, Klinikum der Wolfgang Goethe Universität, Frankfurt au Main, Germany; J. Kurtz, University Hospital, Geneva, Switzerland; H. Mouridsen, Finseninstitutet, Copenhagen, Denmark; M. Piccart, Institut Jules Bordet, Brussels, Belgium; K. Pritchard, Toronto-Sunnybrook Regional Cancer Center, North York, Ontario, Canada; and W. C. Wood, Emory University School of Medicine, Atlanta, GA.

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NOTES

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