Meeting Highlights: Updated International Expert Consensus on the Primary Therapy of Early Breast Cancer

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Abstract: **This account of the highlights of the eighth St Gallen (Switzerland) meeting in 2003 emphasizes new information that has emerged during the 2 years since the seventh meeting in 2001. This article should be read in conjunction with the report of that earlier meeting. Recommendations for patient care are so critically dependent on assessment of endocrine responsiveness that the importance of high-quality steroid hormone receptor determination and standardized quantitative reporting cannot be overemphasized. The International Consensus Panel modified the risk categories so that only endocrine receptor–absent status was sufficient to reclassify an otherwise low-risk, node-negative disease into the category of average risk. Absence of steroid hormone receptors also was recognized as indicating endocrine nonresponsiveness. Some important areas highlighted at the recent meeting include: (1) recognition of the separate nature of endocrine-nonresponsive breast cancer—both invasive cancers and ductal carcinoma-in-situ; (2) improved understanding of the mechanisms of acquired endocrine resistance, which offer exciting prospects for extending the impact of successful sequential endocrine therapies; (3) presentation of high-quality evidence indicating that chemotherapy and tamoxifen should be used sequentially rather than concurrently; (4) availability of a potential alternative to tamoxifen for treatment of postmenopausal women with endocrine-responsive disease; and (5) the promise of newly defined prognostic and predictive markers.**

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DEVELOPMENT OF expert consensus treatment guidelines for early breast cancer requires comprehensive analysis of the results of randomized clinical trials and the interpretation of their biologic, clinical, social, and personal relevance for individual patients. The series of conferences held in St Gallen (Switzerland) since 1978 has specifically focused on reaching expert consensus on the implications of evidence for patient treatment selection.[1] The eighth such meeting, with 3,200 participants from 75 countries, was held in March 2003.

New insight into prognosis and prediction of response has come from the extensive work on the urokinase-type plasminogen activator and plasminogen activator inhibitor type 1 system,[2,3] and recently introduced technologies including gene profiling[4-7] and cyclin E determination.[8,9] However, the exact application of each of these technologies remains to be properly defined.

We finally have reliable evidence that sequential administration of tamoxifen after chemotherapy is superior to concurrent use of these modalities.[10,11] Additional analyses of the National Surgical Adjuvant Breast and Bowel Project (NSABP) study B-20 in node-negative women[12] and the publication of International Breast Cancer Study Group (IBCSG) study IX[13] have clarified that tamoxifen alone may be adequate adjuvant therapy for postmenopausal women with node-negative, endocrine-responsive disease.

Although much useful information will come from new technologies, there is also a valuable resource of information already available from current studies. Subset analysis is inevitable in deriving information with which to tailor treatment to individual patients. Such analysis is statistically proper provided sufficient numbers of patients are available and provided hypotheses generated in one data set can be independently confirmed. This recently has been done to substantiate greater responsiveness to cytotoxic chemotherapy in tumors lacking estrogen receptors,[14,15] and the inadequacy of cytotoxic therapy alone in young patients with endocrine-responsive disease.[16,17] Indeed, concentration exclusively on overall average effects produced by pooling biologically different disease entities can result in dangerously misleading advice for individual patients. Within the Early Breast Cancer Trialists' Collaborative Group Overview of adjuvant cytotoxic therapy,[18] the greater magnitude of benefit observed among older patients with node-negative as distinct from node-positive disease may reflect relative selection into the node-negative cohorts of higher-risk patients with a more chemotherapy-responsive disease associated with lack of steroid hormone receptor expression.[19]

Although preliminary evidence and laboratory models suggest that overexpression of HER2 may indicate a lower probability of responsiveness to tamoxifen[20] and perhaps cyclophosphamide, methotrexate, and fluorouracil (CMF),[21] the Panel was not ready to accept this information as currently useful for patient care. Table 1 describes additional examples of findings presented at the meeting and their implications or status relative to patient care.

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Table 1. Recent Research Findings Presented at the Eighth International Conference on Primary Therapy of Early Breast Cancer and Their Implications for Patient Care

Field or Treatment	Status of Research and Implications for Patient Care
Epidemiology and chemoprevention	With the availability of chemopreventive agents that reduce the risk of developing hormone receptor–positive breast cancer,[22] it becomes important to examine the specific risk factors that predict this type of disease. Factors such as early menarche and delayed menopause, widespread use of hormone replacement therapies, high mammographic density, and obesity (for postmenopausal women only) have been suggested. Familial factors related to *BRCA1* mutations may be more relevant for receptor-negative disease, for which chemoprevention has so far been ineffective.[22,23]
Genetic susceptibility	*BRCA1* and *BRCA2* code for proteins that have an important role in genomic stability,[24] and are responsible for an important minority of familial breast cancers. Treatment decisions for early breast cancer in a mutation carrier need to include consideration of bilateral mastectomy with plastic surgical reconstruction,[25] prophylactic oophorectomy,[26] chemoprevention,[27] and intensified surveillance.[28]
Steroid hormone receptors and modulation of endocrine resistance	There has been rapid progress in understanding the biology of estrogen-receptor function, including its interaction with coactivators and suppressors, the existence and relevance of an extranuclear receptor, and the cross-talk between estrogen receptors and a variety of growth factor signaling pathways.[20,29] This may allow identification of cells unlikely to respond to tamoxifen because of overexpression of AIB1 and HER2. The cross-talk mechanisms provide a number of potential therapeutic targets. Estrogen synthesis blockade by aromatase inhibitors[30,31] or ovarian function suppression[32] may exert their beneficial effects in steroid hormone receptor–expressing cells despite elevated HER2.[20]
Treatment of DCIS	Progress in the understanding of DCIS has largely depended on the recognition of the importance of its hormone receptor status. Tamoxifen is clearly effective in reducing recurrence of receptor-positive DCIS, although there was little evidence of its effectiveness in receptor-negative disease.[33] Additional attention to quality assurance of steroid hormone receptor assays is required.
Surgery for invasive breast cancer	Surgical research has continued to evaluate less radical procedures with the aim of minimizing morbidity while maintaining local control and providing accurate staging and biologic information to guide other treatment modalities.[34,35] Negative axillary SNB is now accepted as allowing avoidance of axillary dissection. Micrometastatic disease in sentinel lymph nodes remains a subject for research, particularly because the prognostic significance of isolated tumor cells (or of tiny clusters) is, at present, unclear.[36] SNB can also be applied to the internal mammary chain, although the therapeutic implications of sentinel node involvement in this area are less certain and are largely experimental.[37]
Radiation therapy in early breast cancer	Breast radiation is clearly indicated after breast-conserving surgery and the role of a boost was recently described, particularly in younger patients.[38] Controversy exists on the timing of radiation therapy with respect to tamoxifen because of some reports on increased lung fibrosis when the two modalities are combined.[39,40] The balance between beneficial and harmful effects of postmastectomy radiation therapy depends on the risk of local recurrence and patient age.[38,41] Radiation therapy confined to fields less than the whole breast (accelerated PBI) has been investigated using a number of different techniques.[42-44] Long-term safety, efficacy and issues about treatment of relapse in the breast after PBI require further proper evaluation.[45] PBI should, for the present, be confined to prospective clinical trials.
Biologic therapies and antibodies	Despite intensive investigations, there are few insights of clinical relevance since 2001. Investigations of adjuvant trastuzumab for patients whose tumors overexpress HER2 are ongoing. Its use in the adjuvant setting outside of clinical trials currently is not justified.
Factors for prediction of treatment responsiveness and prognosis	ER and PgR expression of the primary tumor cells is the only tumor-related marker with clear predictive value for treatment response that has unequivocal clinical utility regarding adjuvant therapy.[46] This central importance of the steroid hormone receptors emphasizes the absolute necessity to measure ER and PgR, report results in a standardized quantitative manner (eg, percent of cells stained), and use quality-assured procedures in experienced laboratories.[47] The predictive utility of HER2 overexpression, cell proliferation markers, and the interaction of these factors with steroid hormone receptor expression await confirmation. The prognostic usefulness of features such as expression of the components of u-PA-PAI1,[2,3] deregulated expression of cyclin E,[8,9] and presence of tumor cells in bone marrow and in circulating blood is likewise uncertain.[46,48,49]
Preoperative (primary, neoadjuvant) systemic therapy	Preoperative systemic therapy, especially chemotherapy, increases the rate of breast-conserving surgery in women presenting with large, unifocal breast cancer. Treatment in the preoperative setting offers unique advantages in understanding the biology of the tumor and its responsiveness to systemic therapy. For example, pathologic complete remission rates to chemotherapy were significantly higher among patients with tumors from which both ER and PgR were absent compared with patients whose tumors had any (even low) expression of steroid hormone receptors.[50,51] Despite potential advantages, preoperative chemotherapy has not been advocated as being preferable to adjuvant (postoperative) chemotherapy because of a lack of demonstrated survival advantage.
Endocrine therapy strategies	The ATAC trial has shown preliminary evidence that anastrozole is superior to tamoxifen as adjuvant therapy for postmenopausal women, 84% of whom had disease recorded as receptor positive.[52] The ASCO Technology Assessment report[53] has recommended that anastrozole be used only for patients in whom tamoxifen is contraindicated or not tolerated. The Panel endorsed this position. In the IBIS chemoprevention trial, tamoxifen increased deep venous thrombosis and pulmonary embolism, especially among patients immobilized by surgery or bone fracture.[27] For premenopausal women with endocrine-responsive disease, ovarian function suppression (goserelin) with[54] or without[55] tamoxifen appeared to be at least as effective as CMF chemotherapy alone. The combination of tamoxifen and GnRH analog was more effective than GnRH analog alone at least in the presence of chemotherapy.[56] The sequential use of goserelin after CMF appeared better than either modality alone in patients with node-negative disease.[57,58] The combination of bilateral oophorectomy followed by tamoxifen was effective compared with no adjuvant treatment even among patients with tumors overexpressing HER2.[32] Chemotherapy alone was insufficient for younger patients with steroid hormone receptor–positive tumors in retrospective analyses conducted in parallel across multiple cooperative groups.[17]

Table 1. Recent Research Findings Presented at the Eighth International Conference on Primary Therapy of Early Breast Cancer and Their Implications for Patient Care (Continued)

Field or Treatment	Status of Research and Implications for Patient Care
Chemotherapy regimens: anthracyclines, taxanes, dose, schedules, duration, and use with tamoxifen	It was recognized that chemotherapy decision making is best based on the principles discussed and published during the last St Gallen conference in 2001. Chemotherapy regimens can be grouped into those of standard efficacy and a small group of regimens and schedules whose efficacy has been shown to be superior to this general level, though usually at the price of additional toxicity, inconvenience, and economical cost. Thus, four courses of AC have been shown to be equivalent to six cycles of classical CMF.[59] On the other hand, Canadian CEF,[60] the CAF regimen,[61] and to some extent tailored FEC,[62] yielded superior results. As with several types and schedules of CMF,[63] it is unlikely that all anthracycline-containing regimens yield similar benefit.[64] Two major trials have examined four courses of paclitaxel after four cycles of AC, but the interpretation of these results has been made difficult by the confounding of duration, receptors, and the concurrent administration of tamoxifen.[65,66] TAC proved superior to FAC in the recent BCIRG trial.[67] More than 20,000 additional women have been included in randomized clinical trials investigating the role of taxanes that have yet to report results.[49] Another concept recently examined in a large randomized trial is that of dose density. Patients receiving the same doses of chemotherapy on a 2-week rather than a 3-week schedule, given to the same total doses, showed superior disease-free and overall survival.[68] These early data must be taken into account with the additional cost of the growth factors required when deciding whether a particular patient should receive her chemotherapy in a dose-dense fashion. Trials that directly examine the role of duration of a single chemotherapy regimen include the French study of FEC for six versus three courses; longer treatment appeared more effective but it is uncertain to what extent this might have been influenced by endocrine effects in this premenopausal population.[69] Additional information is provided by a retrospective pooled analysis of two trials comparing three to six courses of CMF.[70] Except for young patients and those with estrogen receptor–negative tumors, these durations provided similar outcome. It was therefore recognized that questions of chemotherapy duration might be studied preferably in patients whose tumors showed absent steroid hormone receptors, although this does not imply that chemotherapy has no role for patients with tumors containing some steroid hormone receptors. Although different trials have used tamoxifen concurrently with or sequentially after chemotherapy, randomized data were not available until the recent publication of the Intergroup Trial 0100, which elegantly showed the superiority of sequential over concurrent administration for postmenopausal women with node-positive (42% with four or more positive nodes), receptor-positive (ER or PgR) disease.[10,11] Two smaller recently reported studies provide supportive trends.[71,72] No information is available on the concurrent use of aromatase inhibitors and chemotherapy. Tailoring chemotherapy regimens to individual patients needs to take into consideration the trade-off between greater efficacy of certain regimens and the corresponding increase in morbidity, which may or may not be acceptable to particular patients depending on the assessment of the magnitude of incremental benefit.
Psychosocial aspects and patient preferences	It has been recognized that patient preferences are crucial to therapeutic decision making. In general, patients are willing to accept the morbidity typical of adjuvant therapies in return for relatively modest, realistic survival gains.[73] This concept particularly applies to decisions about the addition of chemotherapy to an endocrine regimen that might already offer most of the available improvement in survival, so that the residual potential gain must be evaluated against the morbidity of treatment.

Abbreviations: DCIS, ductal carcinoma in situ; SNB, sentinel lymph node biopsy; PBI, partial breast irradiation; ER, estrogen receptor; PgR, progesterone receptor; u-PA-PAI1, urokinase-type plasminogen activator and plasminogen activator inhibitor type 1; ATAC, Anastrozole, Tamoxifen Alone, or in Combination; ASCO, American Society of Clinical Oncology; IBIS, International Breast Cancer Intervention Study; CMF, cyclophosphamide, methotrexate, and fluorouracil; GnRH, gonadotropin-releasing hormone; AC, doxorubicin and cyclophosphamide; CEF, cyclophosphamide, epirubicin, and fluorouracil; CAF, cyclophosphamide, doxorubicin, and fluorouracil; FEC, fluorouracil, epirubicin, and cyclophosphamide; TAC, docetaxel, doxorubicin, and cyclophosphamide; FAC, fluorouracil, doxorubicin, cyclophosphamide; BCIRG, Breast Cancer International Research Group.

At the conclusion of the conference, an International Consensus Panel of experts (members are listed in the Appendix) was asked, as at the previous conferences,[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 on the basis of the new evidence that has emerged from clinical research since 2001. Although the final table of treatment recommendations will look remarkably similar to that which appeared 2 years ago, the 2003 Panel gave greater emphasis to our ability to identify factors that allow the tailoring of particular treatments to individual patients in the light of patient preference and tumor characteristics.

PROGNOSIS AND PREDICTION OF RESPONSE

Estrogen and progesterone receptor content in the primary tumor are powerful markers to predict endocrine responsiveness in their presence[74] and cytotoxic responsiveness in their absence.[15,19,20,51,75-77] This does not mean that patients with tumors expressing hormone receptors do not benefit from chemotherapy.

Gene expression profiling studies[4-7] support a clear separation of steroid hormone receptor–absent disease as an entity distinct from disease showing low or high levels of receptors, whereas some clinical studies already provide empirical data that receptor-absent disease is different from that with even low levels of receptor expression.[51,75] Most clinical data, however, use a different grouping that combines receptor-absent disease with that expressing low receptor levels (so-called receptor-negative disease). Recognition of the importance of the receptor-absent group will require a change to current practices in many laboratories from reporting merely positive or negative receptor status (often adopting arbitrary cutoffs) in favor of more quantitative reporting of routine receptor determinations.

The implication for tailored treatment advice today depends on the degree of certainty that either modality alone will be

sufficient for an individual patient. At one extreme, patients with both receptors absent can only be treated effectively with chemotherapy. The addition of endocrine agents in this population is at best useless and may be actively harmful either by the direct toxicity of the endocrine agent[22,78,79] or by interference with cytotoxics.[77,80-82] At the other extreme, some patients may have such strong receptor expression that the probability of control with endocrine therapy alone is considered sufficiently high that no cytotoxic treatment is required, especially among patients with low risk for recurrence.[12,13,83] Between these extremes, there is a gradation in level of uncertainty that endocrine therapy alone will be sufficient. In this in-between group, measures of absolute risk (eg, increased nodal involvement), and factors that might predict resistance to tamoxifen (HER2 overexpression) are relative (although imprecise) indications for the addition of cytotoxic therapy. For patients in lower risk groups such as postmenopausal patients in NSABP Trial B-20[12] and IBCSG Trial IX,[13] and premenopausal patients in IBCSG Trial 11–93,[84] endocrine therapy alone may suffice. The Panel considered that, in circumstances in which the need for cytotoxics is uncertain, the addition of other agents such as trastuzumab or the substitution of endocrine agents not affected by a particular form of presumed resistance might reduce the indication for cytotoxics.

In considering stage as a factor that modulates the tailoring of treatment, it is noteworthy that the staging itself is being refined and altered by techniques such as sentinel lymph node biopsy and immunohistochemical identification of tumor cells within lymph nodes (both axillary and other nodes), bone marrow, and circulating blood. The new American Joint Committee on Cancer classification includes patients with isolated tumor cells in lymph nodes as having node-negative status.[85] This may lead to uncertainty about the proper risk category for such patients.

Patient Preferences, Advocacy, and Psychosocial Considerations

As in the previous meeting,[1] the Panel recognized the importance of ascertaining and allowing for patient preferences in defining the threshold of expected benefit at which treatment should be undertaken.[73,86,87] The increasing importance of patient advocacy groups[88-90] and the availability of information on the Internet emphasize the need to incorporate this aspect into decision making. Individual patient's decisions will involve their preferences with regard to the additional benefit that could reasonably be expected from additional effective therapy. Patients should be involved in the decision-making process to the extent they desire[91] and may be assisted by specific decision-making aids.[73,92-94]

CONSENSUS PANEL RECOMMENDATIONS AND GUIDELINES

This section and Tables 2 and 3 summarize the recommendations and guidelines for postoperative adjuvant systemic therapy of early breast cancer proposed by the International Consensus Panel during the St Gallen Conference, 2003. 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, and include expert interpretation of the implications of this evidence for clinical decision making. The guidelines are not intended to be used to define required treatment for all patients because circumstances and attitudes toward treatment and availability of resources may vary both among individuals and systematically in different parts of the world. Discussions on postoperative radiation therapy, preoperative systemic therapy, biologic therapies, and choice of chemotherapy regimen are described within sections of Table 1.

As in previous editions of the Expert Consensus Report, the format used to construct Table 3 reflects the four issues that are considered to make treatment decisions 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 absolute and relative risks and benefits of effective therapies. Aspects related to availability of national resources (for offering every type of adjuvant treatment to all patients in each country) and the involvement of well women in designing

Table 2. Definition of Risk Categories for Patients With Node-Negative Breast Cancer (modified from St Gallen 2001 version)

Risk Category	Endocrine-Responsive Disease*	Endocrine-Nonresponsive Disease*
Minimal risk†	ER and/or PgR ***expressed***, and ***all*** of the following features: pT‡ $\leq$ 2 cm, and Grade§ 1 and Age‖ $\geq$ 35 years	Not applicable
Average risk	ER and/or PgR ***expressed***, and ***at least one*** of the following features: pT‡ $>$ 2 cm, or Grade§ 2–3, or Age‖ $<$ 35 years	ER and PgR ***absent***

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; pT, pathologic tumor size.

*Responsiveness to endocrine therapies is related to expression of ER and PgR in the tumor cells. The exact threshold of ER and PgR staining (with currently available immunohistochemical methods), which should be used to distinguish between endocrine-responsive and endocrine-nonresponsive tumor is unknown. Even a low number of cells stained positive (as low as 1% of tumor cells) identify a cohort of tumors having some responsiveness to endocrine therapies.[95] Probably, as is typical for biologic systems, a precise threshold does not exist. However they are empirically chosen, about 10% positive staining of cells for either receptor might be considered as a reasonable threshold for definite endocrine responsiveness. Furthermore, it is clear that the absence of staining for both receptors confers definite endocrine nonresponsiveness status. This crucial distinction implies the absolute necessity for the reporting of quantitative results of immunohistochemical staining with appropriate quality control.

†Some Panel members recognize lymphatic and/or vascular invasion as a factor indicating greater risk than minimal. Conversely, pure tubular or mucinous histologic types are associated with low risk of relapse.

‡pT indicates the size of the invasive component.

§Histologic and/or nuclear grade.

‖Patients with breast cancer at a young age have been shown to be at high risk of relapse.[96-100]

Table 3. Adjuvant Systemic Treatment for Patients With Operable Breast Cancer

Risk Group	Treatment According to Responsiveness to Endocrine Therapies*			
	Endocrine-Responsive Disease		Endocrine-Nonresponsive Disease	
	Premenopausal	Postmenopausal	Premenopausal	Postmenopausal
Node-negative disease, minimal risk	Tamoxifen or none	Tamoxifen† or none	Not applicable	Not applicable
Node-negative disease, average risk	GnRH analog (or ovarian ablation) + tamoxifen‡ [± chemotherapy§‖], or Chemotherapy§ → tamoxifen‡ [± GnRH analog (or ovarian ablation)], or Tamoxifen, or GnRH analog (or ovarian ablation)¶	Tamoxifen† or Chemotherapy§ → tamoxifen†‡	Chemotherapy	Chemotherapy
Node-positive disease	Chemotherapy → tamoxifen‡ [± GnRH analog (or ovarian ablation)], or GnRH analog (or ovarian ablation) + tamoxifen‡ [± chemotherapy§]	Chemotherapy§ → tamoxifen†‡ or Tamoxifen†	Chemotherapy	Chemotherapy

NOTE. See Table 1 for discussions concerning surgery, radiation therapy, preoperative systemic therapy, biological therapies, and specific chemotherapy regimens.

Abbreviation: GnRH, gonadotropin releasing hormone (research was conducted using goserelin).

*Please see the footnote denoted by the asterisk (*) provided in Table 2, regarding responsiveness to endocrine therapies.

†A 5-year course of tamoxifen remains the standard treatment for women with steroid hormone receptor–positive breast cancer. An aromatase inhibitor (current available data are limited to anastrozole) may be substituted in postmenopausal women in whom tamoxifen is contraindicated or not tolerated.

‡Patients receiving chemotherapy should not start tamoxifen therapy until the completion of chemotherapy.[10,11]

§The threshold for considering addition of chemotherapy to endocrine therapies may depend on the degree of confidence in endocrine responsiveness. Considerations about a low relative risk, age, toxic effects, socioeconomic implications, and information on the patient's preference might justify the use of endocrine therapy alone.

‖Square brackets indicate questions pending answers from ongoing clinical trials.

¶If ovarian function suppression is considered, adding tamoxifen may improve outcome at least in the presence of chemotherapy.[56] The use of GnRH analog alone was shown to be as effective as chemotherapy[55] and may be taken as an adjuvant treatment option in case tamoxifen is not indicated or not desired.

educational strategies (for a more extensive participation of patients in clinical research programs) were discussed, but were not reflected in the recommendations. In countries with limited resources, adjuvant endocrine therapy has been shown to be effective and relatively cost effective.[101]

The most important feature for determination of baseline prognosis remains the nodal status. For women presenting with node-negative disease, two patient populations have been defined on the basis of the risk for relapse (prognosis). These are described in the rows of Table 2 (Minimal risk and Average risk). A subtle but important change introduced to the classification refers to the influence of receptor levels. Only receptor-absent disease is now considered sufficient to constitute a criterion to remove an otherwise suitable patient from the minimal-risk group. This reclassification will avoid placing patients with low levels of receptor expression and otherwise low-risk features into a group for which only chemotherapy would be recommended.[102]

Table 3 lists the categories of therapy considered to be appropriate for each of the groups defined according to treatment response (or predictive) factors. Within the body of Table 3, we distinguish among therapies for which direct evidence is available demonstrating treatment effect on the basis of results of randomized trials and therapies that are still investigational, the latter being indicated with brackets. Footnotes to Table 3 indicate specific additional aspects.

NODE-NEGATIVE BREAST CANCER

Treatment for patients with node-negative disease varies substantially according to the baseline prognosis. For patients considered to be at average risk, the treatment choice follows an algorithm similar to that for node-positive disease. Chemotherapy for approximately six courses was considered to be the treatment of choice for those patients whose tumors did not express estrogen and progesterone receptors, especially those at higher risk of relapse. For those with tumors expressing estrogen and/or progesterone receptors, endocrine therapy alone (adapted to the menopausal status), or combined chemotherapy in association with (usually followed by) endocrine therapy were both considered appropriate treatment options. Definition of the threshold at which combined-modality treatment is preferred may involve consideration of the level of receptor expression and the presence of factors such as HER2 overexpression (and to some extent also high tumor grade or high proliferation rate), which may reduce confidence in the efficacy of endocrine therapy alone.

For patients with minimal-risk disease, the question of whether to treat with tamoxifen depends on a risk-benefit analysis, in which the low relapse rate within the first 10 years and the potential reduction of reappearance of breast cancer in the conserved breast and in the contralateral breast should be taken into account and weighed against risks of endocrine treatment.

NODE-POSITIVE BREAST CANCER

The increased risk of relapse and death associated with tumor metastasis to the ipsilateral axilla has in the past significantly influenced the choice of treatment. More intensive cytotoxic courses of treatment were used to attempt a more extensive tumor-cell kill. Even with endocrine-responsive disease, the higher risk of relapse and the presence of endocrine-resistant clones within the tumor, in general, have been taken as indications for the inclusion of cytotoxic chemotherapy in the treatment regimen.

The Panel recognized two general levels of cytotoxic therapy regimens, as discussed in Table 1. Treatment with four courses of doxorubicin and cyclophosphamide was shown to be equivalent to six courses of classical CMF.[59] Several regimens and schedules, such as Canadian cyclophosphamide, epirubicin, and fluorouracil (Canadian CEF)[60]; the cyclophosphamide, doxorubicin, and fluorouracil (CAF) regimen[61]; dose-dense administration of doxorubicin, paclitaxel, and cyclophosphamide[68]; and also to some extent, tailored fluorouracil, epirubicin, and cyclophosphamide (FEC),[62] and docetaxel, doxorubicin, and cyclophosphamide (TAC)[67] have been shown in comparative trials to yield superior results, though at the cost of greater complexity, economic cost, or toxicity (Table 1). These more effective regimens may be preferred in patients at higher risk.

SPECIFIC ASPECTS OF TREATMENT

Ovarian Ablation and Ovarian Endocrine Function Suppression

The Early Breast Cancer Trialists' Collaborative Group Overview results[103] indicated a beneficial effect of ovarian ablation. This treatment significantly improved long-term survival for women younger than 50 years of age, at least in the absence of chemotherapy.[56] Long-term side effects, mainly for young women, are still a significant issue when this treatment is offered especially because the safety of treatments for menopausal symptoms is unknown.

For premenopausal women with endocrine-responsive disease, ovarian function suppression (goserelin) with[54] or without[55] tamoxifen appeared to be at least as effective as CMF chemotherapy alone, and information is available that the addition of tamoxifen to goserelin is more effective than goserelin alone, at least in the presence of chemotherapy.[56] The sequential use of goserelin after CMF appeared better than either modality alone in patients with node-negative disease, at least in subset analyses for women with estrogen receptor–positive breast cancer and those younger than 40 years.[57] The combination of bilateral oophorectomy followed by tamoxifen was effective compared with no adjuvant treatment even among patients with tumors overexpressing HER2.[32] Chemotherapy alone was insufficient for younger patients ($<$ 35 years of age) with steroid hormone receptor–positive tumors in retrospective analyses conducted in parallel across multiple cooperative groups,[17] presumably because such patients received inadequate endocrine therapy from the ovarian effects of their cytotoxic treatment.

Aromatase Inhibitors in Postmenopausal Patients

A large randomized clinical trial (ATAC: Anastrozole, Tamoxifen Alone, or in Combination) has shown preliminary evidence that anastrozole is superior to tamoxifen as adjuvant therapy for postmenopausal women, 84% of whom had disease recorded as receptor-positive.[52] The combination was no more effective than tamoxifen alone. The toxicity profile was more favorable with anastrozole with the exception of an increased risk of musculoskeletal disorders and bone fractures. Tamoxifen has a long-lasting (carryover) benefit,[74] so that the ultimate comparison between these two agents must await additional follow-up. Thus, long-term superiority of anastrozole is uncertain. An additional concern is that unplanned subset analyses within the ATAC trial have indicated less effect for anastrozole among groups defined by prior radiation therapy (63% of patients) or chemotherapy (21% of patients). Results from retrospective studies, on material from two distinct trials comparing tamoxifen with letrozole[30] or anastrozole,[31] indicate that aromatase inhibitors are more effective than tamoxifen in patients with disease expressing estrogen receptors or progesterone receptors in the presence of overexpressed HER2. This observation must still be prospectively confirmed. Accordingly, the American Society of Clinical Oncology Technology Assessment Report[53] has recommended that anastrozole be used only for postmenopausal patients in whom tamoxifen is contraindicated or not tolerated, and the St Gallen Panel agreed with this statement. In making this assessment, it is noteworthy that the NSABP P-1 and the International Breast Cancer Intervention Study (IBIS-I) chemoprevention trials found that tamoxifen increased deep venous thrombosis and pulmonary embolism, especially among patients immobilized by surgery or bone fracture.[78,79]

Radiation Therapy in Early Breast Cancer

Recent analysis of the Danish and the European Organization for Research and Treatment of Cancer trials has cast doubt on the traditional perception that radiotherapy is relatively of most benefit to patients with higher risk of relapse (eg, four or more positive nodes). In these trials the highest survival benefit was seen predominantly among patients with one to three positive nodes, whereas the reduction in locoregional recurrences was largest in patients with more advanced cancer.[104] Tailoring postmastectomy radiation therapy treatment recommendations for individual patients remains a priority for additional research.

COMMENTARY

The International Consensus Panel attempted to answer many questions related to the best use of treatments investigated in randomized clinical trials. New available information from clinical trials enhanced the role of endocrine treatments, especially in premenopausal women, for whom the endocrine effects of cytotoxics was also evident. The Panel members were more than ever convinced that much more can be achieved to increase knowledge about the disease and im-

prove patient care, if participation in clinical trials were to become more acceptable to the public and the medical community.[105] International cooperation on trials and their evaluation must concentrate on the investigation of critical biologic principles rather than merely establishing the superiority of particular pharmaceuticals for regulatory purposes. A collaborative approach involving the development of new agents and their careful scientific study by investigator-controlled clinical trials groups to determine their optimal integration into adjuvant therapy programs will best ensure progress for improved patient care. Patients with early breast cancer deserve no less.

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APPENDIX

The appendix is included in the full text version of this article only, available on-line at www.jco.org. It is not included in the PDF version.

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