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

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DEVELOPMENT OF treatment guidelines for early breast cancer requires comprehensive analysis of the results of randomized clinical trials and the interpretation of their biologic, clinical, and social relevance for individual patients. Several successive worldwide meta-analyses, using available data from individual randomized trials, have been presented by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).[1-5] Conferences such as the series that have been held in St Gallen, Switzerland, since 1978 provide an opportunity to reach expert consensus about the implications of these and other relevant data to guide women and their doctors in the selection of appropriate treatment.

In February 2001, the Seventh International Conference on Adjuvant Therapy of Primary Breast Cancer was held in St Gallen, Switzerland. Knowledge on breast cancer genetics, diagnosis, treatment, and prevention has evolved since the Sixth International Conference, held in February 1998.[6] Some important areas highlighted at the recent meeting include recognition of the increased role of endocrine therapy in properly selected patient groups, the loss of enthusiasm for high-dose therapy and incorporation of new agents to be reflected in improved outcomes, the avoidance of unnecessarily extensive surgery by development of sentinel lymph node biopsy, a better definition of the role of postmastectomy radiation therapy, and the importance of factoring patient preferences into treatment decisions. Table 1 describes some examples of findings presented at the meeting and their implications or status relative to patient care.

At the conclusion of the conference, a Consensus Panel of experts was asked, as at the previous conferences,[6] 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. Overall, the Panel developed a simplified classification of risk and highlighted the factors governing selection of adjuvant endocrine and cytotoxic therapies. Considerations on postoperative radiation therapy as well as aspects of preoperative systemic treatments and use of biologic compounds were also discussed.

PROGNOSIS AND PREDICTION OF RESPONSE

An important change from previous years is that the Panel no longer defines a group of patients who should not be offered adjuvant systemic therapy. Even among patients who are at minimal or low risk of recurrence (10% recurrence at 10 years; Table 2), a case can be made for adjuvant tamoxifen to prevent a second primary breast cancer by analogy with the Breast Cancer Prevention Trial (National Surgical Adjuvant Breast and Bowel Project P-1)[17] and the overview by the EBCTCG.[3] Reduced incidence of second breast cancers in women receiving tamoxifen was confined to the cohorts with tumors expressing steroid hormone receptors, whereas no reduction in incidence was observed for patients who had tumors without such receptors.

The most relevant factors for the estimation of risk of recurrence remain the nodal status and the number of nodes involved. For patients with node-negative presentation, pathologic tumor size, histologic and nuclear grade, and age are factors considered to define differential prognosis (Table 2). Although all patients with involved nodes are at high risk, there remains a gradient of absolute risk of recurrence and therefore of absolute benefit from adjuvant therapy as the number of involved axillary lymph nodes increases.

An additional fundamental change from the previous consensus is that treatment selection is based primarily on assessment of endocrine-responsive or endocrine-nonresponsive disease according to the presence of estrogen and progesterone receptors in the primary tumor. The threshold defining endocrine-responsive disease has also changed in that tumors containing as few as 1% of cells staining for steroid hormone receptors are regarded as potentially endocrine-responsive (ie, might benefit from the addition of endocrine therapies to the adjuvant treatment program). Selection of endocrine therapy alone, chemotherapy alone,

Table 1. Recent Research Findings Presented at the Seventh 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, environmental, and nutritional features	New data based on comparison of identical and nonidentical twins suggested that as much as 27% of breast cancer may be due to inheritable factors,[7] which is higher than previous estimates based on population studies.[8] Many of the lifestyle, nutritional, and environmental risk factors are related to endocrine features (eg, it is suggested that increased free estradiol associated with obesity and alcohol consumption may be responsible for the observed increased risk).[9,10]
Genetics: susceptibility genes	BRCA1 and BRCA2 code for proteins that have an important role in genomic stability.[11] It is estimated that mutations of these two genes contribute only 30% to 40% of hereditary susceptibility to breast cancer, implying the existence of undiscovered susceptibility genes. Because screening such women has proved to be difficult, prophylactic strategies to reduce breast cancer risk include mastectomy,[12] which is at least 90% effective, and oophorectomy.[13-15] Oophorectomy also reduces by 50% to 70% the risk of breast cancer in families prone to breast and ovarian cancer, reducing significantly the risk of occurrence of the latter as well.[16] BRCA1 tumors are usually estrogen receptor–negative, so it is unknown whether tamoxifen prevention will reduce incidence of breast cancer in mutation carriers.[17-19] Information on risks associated with the use of hormone replacement therapy is not available. There is evidence that women genetically predisposed to breast cancer may be more susceptible to the further increase in risk associated with oral contraceptives.[20]
Chemoprevention	Several large randomized trials have reported on the role of tamoxifen in breast cancer prevention,[17,18,21] whereas another has yet to be reported.[22] Meta-analysis of available data is consistent with a substantial reduction in early breast cancer incidence, apparently confined to tumors expressing estrogen receptor.[23] Unresolved questions include the role of tamoxifen in women carrying high-risk genetic mutations[24,19] and a possible interaction with hormone replacement therapy.[21] Also fenretinide, a vitamin A analog, has shown some beneficial effect in premenopausal women.[25] Further testing of retinoids is required before any proposed use outside the framework of clinical trials is to be considered.
Steroid hormone receptors and SERMs	Improved understanding of the estrogen receptor mechanism may follow from the discovery of estrogen receptor beta,[26] although its precise role remains to be determined.

SERMs vary in the length and shape of a critical side chain, which influences their interaction with the estrogen receptor.[27] Raloxifene, for example, binds less efficiently than tamoxifen in experimental models. Fulvestrant interacts quite differently with the estrogen receptor, leading to its destruction rather than to its inactivation. Raloxifene and fulvestrant should not be proposed as a substitute for tamoxifen unless this is done within the context of a controlled clinical trial. |
| Treatment of ductal carcinoma-in-situ | Data from randomized trials have not defined any group of patients with DCIS that will not obtain some relative risk reduction both by radiation therapy and tamoxifen.[28-31] Because the absolute risk of recurrence (in situ or invasive) is very low, the small absolute benefits must be weighed against the inconvenience and morbidity of the interventions (ie, radiation therapy, tamoxifen). The relative prognostic roles of tumor size, margin width and clearance, grade, comedonecrosis, and age for treatment recommendations[32] remain to be confirmed.

The general recommendations for local treatment have not changed during the past 3 years. Conservation of the breast should be attempted when possible and desired. Formal axillary dissection is not indicated. In patients with large, high-grade DCIS lesions diagnosed by needle biopsy in whom mastectomy might be necessary, consideration should be given to sentinel node biopsy or axillary dissection, because there is a significant possibility that invasion will be identified when the lesion is completely examined. |
Surgery for invasive breast cancer	Recent new trends in surgical management relate to the approaches to the primary tumor and to the axilla. Surgery for primary invasive breast cancer include increasing acceptance of immediate reconstruction in cases where mastectomy is required. An important development relates to the extensive investigation of axillary staging by SNB, changing the surgical approach by potentially reducing the number of patients who require axillary lymph node dissection. In experienced surgical hands and with proper pathologic work-up, the finding of a negative sentinel node (with sensitivity and specificity being > 90%) may safely avoid an axillary lymph node dissection. Controversy remains about the routine use of SNB and the degree of surgical expertise required to safely and effectively use this procedure.[33-35] The role of immunohistochemistry and the significance of detected micrometastatic disease in sentinel lymph nodes require further investigation.[36] There is no consensus about whether immunohistochemically detected tumor cells should be regarded as proof for node-positive disease.
Radiation therapy in early breast cancer	Breast radiation is clearly indicated after breast-conserving surgery. A meta-analysis supports the benefit of radiation therapy after mastectomy in terms of reduction of local and regional recurrence and of breast cancer mortality.[5] Radiation therapy was associated with an increase in late mortality from causes other than breast cancer. Although this is less evident in more recent trials, information on late adverse effects remains limited. The balance between beneficial and harmful effects of postmastectomy radiation therapy depends on the risk of local recurrence and perhaps patient age.[5,37] Postmastectomy radiation is indicated for patients who are at high-risk of local recurrence (eg, 20% or more, as those presenting with four or more metastatic axillary lymph nodes, and some patients with pT3 presentation). The role of postmastectomy radiation therapy for patients with one to three involved axillary lymph nodes is being investigated in clinical trials. The safety of local and regional radiation therapy given after anthracyclines and/or taxanes remains uncertain.
Biologic therapies and antibodies	A large number of new agents exploiting advances in understanding of molecular biology and targeting are approaching clinical trial. So far, the major contribution has come from a humanized monoclonal antibody to HER2/neu, a member of the EGF receptor family.[38,39] Trastuzumab has been shown to be effective both as a single agent and in combination with cytotoxic chemotherapy in the treatment of metastatic breast cancer overexpressing HER2/neu. Several large randomized trials are addressing the role of trastuzumab in the adjuvant setting, and its use outside the context of a clinical trial should be avoided. Promising agents, including tyrosine kinase modulators, modulators of EGF receptor, and compounds that inhibit neoangiogenesis, are all at various stages of investigation.

Table 1. (Cont'd)

Field or Treatment	Status of Research/Implications for Patient Care
Factors for prediction of treatment responsiveness	The steroid hormone receptor status of the primary tumor is the only tumor-related marker of treatment response that has unequivocal clinical utility. Immunohistochemistry yields tighter prediction for endocrine therapy responsiveness than older ligand-binding assays. Even minimally detectable hormone receptors are useful for such prediction.[40]
	The utility of HER2/*neu* overexpression, cell proliferation markers, and the interaction of these factors with steroid hormone receptor expression for predicting response to systemic therapies await confirmation.
Preoperative (primary, neoadjuvant) systemic therapy	The role of preoperative chemotherapy has not been further defined since the last report. Outside clinical trials, such treatment seems indicated only for patients with locally advanced disease or those in whom a reduction of primary tumor size may allow breast conservation. Preoperative endocrine therapy with letrozole was more effective than tamoxifen in a single randomized trial in postmenopausal patients.[41] This observation awaits further confirmation on the role of primary endocrine therapy.
Endocrine therapy strategies for younger patients	Chemotherapy alone is insufficient for younger patients with steroid hormone receptor–positive tumors, perhaps because cytotoxic regimens do not effectively suppress ovarian function in this age group.[42] Endocrine therapy, including ovarian suppression with GnRH analog and tamoxifen, is at least equal to conventional cytotoxic chemotherapy, as shown in several large randomized clinical trials.[43-46] In advanced disease, the combination of GnRH analog and tamoxifen yields better disease control than either alone.[47] In the adjuvant setting, no benefit has been shown from adding chemotherapy to combined endocrine therapy (ovarian ablation/suppression plus tamoxifen) in a small trial of premenopausal patients with receptor-positive tumors.[48] This observation does not imply that chemotherapy should be avoided for premenopausal patients with tumors expressing estrogen and/or progesterone receptors, but rather that further research is required to define the role of ovarian function suppression together with tamoxifen after the use of chemotherapy for endocrine-responsive disease.
Chemotherapy regimens: anthracyclines, taxanes, dose, schedules, timing, and duration	On average, anthracycline-containing chemotherapy regimens provide additional benefit compared with nonanthracycline regimens (primarily a variety of CMF schedules) in a meta-analysis.[4] There is evidence that classical CMF[49] is superior to some commonly used variants of CMF[50,51] included in the meta-analysis. The small additional benefit of anthracycline-containing regimens must be balanced against their specific toxicities. A recent report on long-term cardiac effects of doxorubicin showed no significant cardiac clinical sequelae that counter-balanced the benefit of adjuvant treatment.[52]
	The use of paclitaxel after an anthracycline-based regimen became popular after early results from a single large randomized trial.[53] The early benefit was not maintained with additional follow-up, and results from another large randomized trial of almost identical design showed no significant benefit from the addition of paclitaxel. Subset analyses suggest that any benefit might be confined to patients with receptor-negative tumors. In both trials, the regimen including paclitaxel was of longer duration, which might be particularly relevant in such patients.[54,55]
	Four randomized trials of high-dose chemotherapy requiring stem-cell support[56-59] have been reported. The overall results of these trials do not demonstrate any superiority for the high-dose regimen compared with control regimens not requiring stem-cell support.
	The early initiation of chemotherapy after surgery seems to be beneficial for patients with endocrine-nonresponsive disease.[60] Also, the use of cytotoxics for a longer duration (eg, six courses compared with three courses of classical CMF) seems to be beneficial for this subpopulation.[55,61]
	Endocrine therapy (tamoxifen) is not indicated in patients whose tumors do not express steroid hormone receptors and may indeed be deleterious if given with chemotherapy to such patients.[62,63]
Evidence from the overview 2000	The worldwide meta-analysis of adjuvant therapies in early breast cancer was updated in September 2000. This meta-analysis provides powerful evidence for the presence of a therapeutic benefit for chemotherapy, tamoxifen, ovarian ablation, and radiation therapy, although the homogenization inherent in the process limits its ability to estimate the magnitude of the benefit of particular treatments in defined patient groups. It is clear that the magnitude of the benefit of tamoxifen is greatest among patients with estrogen receptor–positive tumors who receive at least 5 years of tamoxifen treatment. Because this is now the standard of care for such patients, it is appropriate to evaluate the magnitude of benefit of tamoxifen solely from this small subset of patients in the tamoxifen overview. It may be important to adopt a similar approach to estimating the magnitude of chemotherapy benefits separately in populations for which chemotherapy alone or in combination with endocrine therapy may be the current treatment of choice.
Psychosocial aspects	Several studies have examined patient preferences concerning the additional benefits required to justify adjuvant systemic therapy. All studies agree that women would accept standard cytotoxic chemotherapy regimens for very modest improvements in outcome.[64-66] By contrast, one study reported that premenopausal women required much larger improvements in outcome to justify adjuvant endocrine therapy. These results call into question the usual assumption that endocrine therapies are perceived by women as less toxic than chemotherapy.[67]
	Quality-of-life measures were frequently of prognostic value in metastatic disease but no such association could be demonstrated in the adjuvant setting.[68]

Abbreviations: SERMs, selective estrogen receptor modulators; DCIS, ductal carcinoma-in-situ; SNB, sentinel lymph node biopsy; EGF, epidermal growth factor; GnRH, gonadotropin-releasing hormone; CMF, cyclophosphamide, methotrexate, and fluorouracil.

or of the combination of these modalities depends upon a complex integration of factors, including assessment of risk of recurrence and the probability of endocrine responsiveness. Thus, for example, a patient with uninvolved or only a few involved lymph nodes and a strongly positive receptor tumor (eg, 90% of cells stained), might best be treated with endocrine therapy alone, whereas a patient with multiple involved nodes and a low level of detectable receptor (eg,

Table 2. New Definition of Risk Categories for Patients With Node-Negative Breast Cancer

Risk Category	Endocrine-Responsive*	Endocrine-Nonresponsive*
Minimal/low risk†	ER- and/or PgR-positive, and all of the following features: pT‡ ≤ 2 cm, and Grade 1§, and Age∥ ≥ 35 years	Not applicable
Average/high risk	ER- and/or PgR-positive, and at least one of the following features: pT‡ > 2 cm, or Grade 2-3§, or Age∥ < 35 years	ER- and PgR-negative

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor.

*Responsiveness to endocrine therapies is related to expression of ER and PgR in the tumor cells. The exact threshold of ER and/or 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.[40] Probably, as is typical for biologic systems, a precise threshold does not exist. However empirically chosen, approximately 10% positive staining of cells for either receptor might be considered as a reasonable threshold, accepted by most. Furthermore, it is clear that the lack of staining for both receptors confers endocrine nonresponsiveness status.

†Some Panel members recognize lymphatic and/or vascular invasion as a factor indicating greater risk than minimal or low. On the other hand, mucinous histologic type is associated with low risk of relapse.

‡Pathologic tumor size (ie, size of the invasive component).

§Histologic and/or nuclear grade.

∥Patients with breast cancer at young age have been shown to be at high risk of relapse.[41]

9% of cells stained) would probably be a candidate for combined chemoendocrine therapy. Uncertainty remains regarding the value of factors such as overexpression of HER2/*neu*, *p53* mutation, and high level of proliferative markers for selecting patients for combined therapy.[69] Patients with endocrine-nonresponsive disease (absence of detectable steroid hormone receptors) should be offered adjuvant chemotherapy alone. Such patients do not benefit from adjuvant endocrine therapy. Indeed they should not receive endocrine therapy, because this may in some circumstances reduce the efficacy of their adjuvant chemotherapy.

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, 2001. 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, as circumstances and attitudes toward treatment and resources may vary both between 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 Experts' Consensus, the format used to construct Table 3 reflects the four issues that are considered during treatment decision made 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 in each country), and the involvement of well women in designing educational strategies (for a more extensive participation of patients in clinical research programs) were discussed but were not reflected in the recommendations.

The most important feature for determination of baseline prognosis is the nodal status. For women presenting with node-negative disease, two patient populations have been defined, based on the risk for relapse (prognosis). These are described in the rows of Table 2 (minimal/low-risk and average/high-risk). Table 3, which defines the types of therapy considered to be effective, is based on different treatment response (or predictive) factors. These include steroid hormone receptor status of the primary tumor and the opportunity to add ovarian function suppression as a therapeutic modality (premenopausal *v* postmenopausal status). The specific treatment recommendation for elderly patients (specifically referred to in previous editions of the conference) was felt to be arbitrarily created and not useful for treatment choice. Considerations concerning tradeoffs among burdens of treatment (eg, undesired toxic effects), potential to reduce the absolute risk of relapse, and competing causes of morbidity and mortality are thus to be applied in each age group.

Within the body of Table 3, we distinguish between therapies for which direct evidence is available demonstrating treatment effect based on results of randomized trials and therapies that are still investigational, the latter being indicated with brackets. Finally, footnotes to Table 3 indicate specific areas in which patient preference should be considered to define appropriate treatment. As previously emphasized, physicians should elicit preferences of patients

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

| Risk Group | Treatment According to Responsiveness to Endocrine Therapies† | | | |
| | Endocrine-Responsive | | Endocrine-Nonresponsive | |
	Premenopausal	Postmenopausal	Premenopausal	Postmenopausal
Node-negative, minimal/low risk	Tamoxifen or none	Tamoxifen or none	Not applicable	Not applicable
Node-negative, average/high risk	Ovarian ablation (or GnRH analog) + tamoxifen [± chemotherapy‡], or Chemotherapy + tamoxifen‡ [± ovarian ablation (or GnRH analog)] or Tamoxifen, or Ovarian ablation (or GnRH analog)	Tamoxifen, or Chemotherapy + tamoxifen‡	Chemotherapy[§]	Chemotherapy[§]
Node-positive	Chemotherapy + tamoxifen‡ [± ovarian ablation (or GnRH analog)], or Ovarian ablation (or GnRH analog) + tamoxifen [± chemotherapy‡]	Chemotherapy + tamoxifen,‡ or Tamoxifen	Chemotherapy[§]	Chemotherapy[§]

NOTE. Brackets [ ] indicate questions pending answers from ongoing clinical trials. Regarding GnRH, research was conducted using goserelin.

*See Table 1 for discussions concerning radiation therapy, preoperative systemic therapy, biologic therapies, and specific chemotherapy regimens.

†See footnote (denoted by *) in Table 2 regarding responsiveness to endocrine therapies.

‡The addition of chemotherapy is considered an acceptable option based on evidence from clinical trials. Considerations about a low relative risk, age, toxic effects, socioeconomic implications, and information on the patient's preference might justify the use of tamoxifen alone. For patients with endocrine-responsive disease, whether tamoxifen should be started concurrently with chemotherapy or delayed until the completion of chemotherapy must await the results of ongoing trials.

§For patients with endocrine-nonresponsive disease, questions of timing, duration, agent, dose, and schedules of chemotherapy are subjects for research studies.

concerning aversion to side effects and attitudes toward disease recurrence and weigh these preferences against the uncertainty about prognosis and treatment effectiveness in terms of the absolute magnitude of the benefit to be achieved. The recommendation to consider patient preference does not mean that when physicians are uncertain about what to do they should invite the patient to decide. Rather, the footnotes emphasize that physician's judgment based on patient preference is an acceptable way to help in the selection of adjuvant treatment.

NODE-NEGATIVE BREAST CANCER

Treatment for patients with node-negative disease varies substantially according to the baseline prognosis. For patients considered at high risk, the treatment choice follows an algorithm similar to that for node-positive disease, considering mainly resistance or responsiveness to endocrine therapies (ie, the latter requires presence of positive estrogen and/or progesterone receptor staining at the histopathologic evaluation of the primary tumor). 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 fol-

lowed by) endocrine therapy were both considered appropriate treatment options.

- Data from individual clinical trials on the treatment of patients with node-negative disease indicate that the addition of classical CMF (cyclophosphamide, 100 mg/m^2 orally, daily on days 1 through 14; methotrexate 40 mg/m^2 administered intravenously [IV] and fluorouracil 600 mg/m^2 IV, both on days 1 and 8, repeated every 4 weeks[49]) or of methotrexate followed by fluorouracil (M-F) to tamoxifen benefited the patients as compared with tamoxifen alone.[70]

- Additional information from a trial conducted specifically in postmenopausal patients leads to the conclusion that much of the effect of chemotherapy (three courses of classical CMF) is seen in patients with low or no estrogen receptor expression in the primary tumor.[71]

- The use of an adjuvant anthracycline-based regimen is probably indicated in the high-risk, node-negative setting. The choice of the regimen should especially account for the results from two trials in which classical CMF was compared with an anthracycline combination. In one trial, a CMF-like anthracycline regimen (CAF, in which cyclophosphamide is given orally on days 1 through 14, and doxorubicin and fluorouracil, both IV, are given on days 1 and 8 of a 28-day course) was shown to improve outcome when compared with

classical CMF,[72] whereas in the other, in which AC (doxorubicin plus cyclophosphamide IV on day 1 every 21 days) was used, no difference in treatment outcome was seen.[73]

- The use of tamoxifen is not indicated for patients with hormone receptor status defined as negative.[3,73]

For patients with minimal/low-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 the incidence of breast cancer in the conserved breast and in the contralateral breast should be taken into account and weighed against risks of endocrine treatment.

- The use of ovarian function suppression for a limited period of time (eg, 2 years of gonadotropin-releasing hormone [GnRH] analog) is being investigated, and preliminary results are encouraging.[74]
- The use of chemotherapy was not considered a reasonable option for this group of patients, although information is available on the efficacy of adjuvant chemotherapy in reducing the risk of relapse, mainly in premenopausal patients.[75] How much of this benefit is due to the endocrine effects of chemotherapy is still a matter for research.[76,77]

NODE-POSITIVE BREAST CANCER

The increased risk of relapse and death associated with tumor metastasis to the ipsilateral axilla had 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. The higher risk of relapse represents, in fact, a larger opportunity for a greater absolute benefit, because most evidence supports a similar proportional benefit in higher- and lower-risk groups. Some areas of research provided useful information for making treatment recommendations for patients who are at an increased risk of relapse.

- The use of anthracycline-based regimens led, on average, to improved treatment results compared with CMF-type regimens.[4] Direct comparison of an anthracycline-based regimen with classical CMF showed a significant improvement in disease-free survival favoring the former almost exclusively in trials in which the schedule of the anthracycline-based regimen was similar to classical CMF (eg, CEF, which is a 4-epidoxorubicine–containing regimen, and CAF, which is a doxorubicin-containing regimen).[72,78] These data are the basis for indicating a preference for anthracycline regimens in this setting.
- Several trials of high-dose chemotherapy with marrow or peripheral-blood progenitor-cell support failed to show a significant improvement in treatment outcome.[56-59] Some studies of high-dose chemotherapy are still under evaluation and their results will become available shortly. At this stage it is unknown whether clinically relevant reduction of relapse rates or mortality will derive from high doses of cytotoxics requiring stem-cell support, and the use of this modality should be exclusively confined to the framework of randomized clinical trials.

- An initial wave of enthusiasm followed the early results of a large trial investigating the introduction of taxanes, specifically paclitaxel, as part of a standard adjuvant therapy for node-positive breast cancer.[53] Further follow-up of that trial and the presentation of a second trial, with a similar design and size, suggested that the addition of paclitaxel after four courses of AC might be effective only in patients with endocrine-nonresponsive disease. There was no apparent benefit of paclitaxel among patients who were treated also with tamoxifen. Furthermore, because paclitaxel extended the duration of adjuvant chemotherapy, doubt remains in terms of whether a taxane would add benefit if comparing two cytotoxic regimens of the same duration (ie, four courses of AC followed by four courses of paclitaxel *v* AC followed by another effective regimen of similar duration) for patients with endocrine-nonresponsive disease.[54] Investigations on the role of taxanes (paclitaxel and docetaxel) in adjuvant cytotoxic regimens are ongoing and will provide useful information on the use of these drugs. The most important information from the first trial of paclitaxel as part of the adjuvant chemotherapy program[53] is probably related to the essential role of endocrine treatment in addition to a short course (AC for four cycles) for patients who are at high risk of relapse but who have endocrine-responsive disease.
- Combined chemotherapy and tamoxifen was proven to be superior to tamoxifen alone in several individual trials of patients with tumors expressing estrogen and/or progesterone receptors, and this is well reflected in the overview.[3,4] The higher the risk of relapse, the larger might be the advantage of the chemotherapy plus tamoxifen over tamoxifen alone. The recommendation on the use of tamoxifen alone in postmenopausal women with node-positive disease may be justified on the basis of individual considerations related to risk of relapse, age, and assessment of patient's preference.

<center>SPECIFIC ASPECTS OF TREATMENT</center>

Ovarian Ablation and Ovarian Endocrine Function Suppression

The overview results[2] indicated the beneficial effect of ovarian ablation. This treatment significantly improved long-term survival for women younger than 50 years, at least in the absence of chemotherapy. Long-term side effects are still a significant issue when offering this treatment mainly to very young women, especially because the safety of treatments for menopausal symptoms is unknown for this cohort of patients.

Seven trials (most with only preliminary data) tested the use of goserelin to suppress ovarian function (with or without the addition of tamoxifen), comparing it with chemotherapy alone.[43-46,74,79,80] The addition of goserelin to chemotherapy, with or without tamoxifen, was tested in the Intergroup Trial 0101.[79] The results led to the conclusion that, after chemotherapy, the combination of goserelin with tamoxifen is more effective than goserelin alone in terms of disease-free survival (but not in terms of overall survival). Tamoxifen alone was not tested. The most relevant question remains, in fact, whether premenopausal patients who maintain ovarian endocrine function after chemotherapy should be offered tamoxifen alone, or tamoxifen plus ovarian suppression. Data from randomized trials in advanced disease suggest that combined tamoxifen and GnRH analog is indeed more beneficial than each of the modalities alone.[47] On the basis of available information from the randomized trials in the adjuvant setting, it is clear that combined tamoxifen and GnRH analog may be regarded as a proper treatment option for premenopausal women with endocrine-responsive disease. The duration of GnRH analog treatment has not been critically studied, and in the various trials, the drug was given for 2, 3, or 5 years.

Tamoxifen

Tamoxifen is the most established adjuvant treatment for patients with tumors expressing steroid hormone receptors.[3] Its use for the duration of 5 years seems to reduce relapse and death, with benefit accruing for several years after its cessation (the term of carry-over effect has been conceived at the EBCTCG secretariat to describe this observation). The question of whether a longer duration of treatment with the drug will improve treatment outcome is under investigation in at least two large randomized trials. The late use of tamoxifen (beginning treatment some years after diagnosis) has been shown in a randomized controlled trial[81] to be effective in women with endocrine-responsive disease who did not start the drug shortly after surgery.

Despite the fact that tamoxifen has been widely used for almost three decades, the relevance of its endocrine effects also on other target tissues has not been completely elucidated. As described above, it is as yet unknown whether ovarian function suppression in premenopausal patients treated with adjuvant tamoxifen significantly improves treatment outcome. In postmenopausal patients, an important question is whether the association of tamoxifen with aromatase inhibitors, especially their sequential use, improves treatment results. This has been suggested in a small trial in which aminogluthetimide in sequence after tamoxifen was used.[82] This information, together with the data of efficacy of newer aromatase inhibitors, such as anastrozole, letrozole, and exemestane, on measurable disease (mostly advanced disease; in one trial of letrozole was tested as a neoadjuvant treatment), awaits confirmation in ongoing trials in the adjuvant setting. Their use is not indicated outside the framework of clinical trials. The Panel stressed that the use of other selective estrogen receptor modulators instead of tamoxifen or after the treatment of this drug is currently not justified, given available data.

Chemotherapy Regimen

Anthracycline-based regimens have been increasingly introduced to clinical practice, motivated by the evidence that, on average, their use is more effective in terms of relapse-free and overall survival than several CMF-based regimens (see also discussion within the sections on treatment of node-negative and node-positive disease).[4] The optimal dose of anthracyclines (doxorubicin and epirubicin) for inclusion in such regimens is unknown, although some information on reduced treatment effects with a lower anthracycline dose is available.[83,84] Increasing the dose of doxorubicin did not improve treatment results in a trial in which the role of paclitaxel was also investigated.[53] An important observation related to the use of intensive regimens containing anthracyclines and alkylating agents, often with the support of hemopoietic growth factors, is the increased incidence of leukemia.[57,78]

The failure to show a clinically relevant treatment effect using high-dose chemotherapy (with marrow or peripheral-blood progenitor-cell support) represents a challenge for development of newer regimens, with particular attention on predictive factors and focusing on patients with disease likely to have less interference with endocrine effects of chemotherapy. Also the inconclusive evidence on the usefulness of taxanes in the adjuvant setting leads to similar conclusions.

Progress in cytotoxic adjuvant therapy has been limited. Indeed, an old regimen such as classical CMF remains a valid treatment alternative for patients with lower risk of

relapse. One potentially promising approach is the combined use of trastuzumab and chemotherapy,[38] which is being investigated in at least five clinical trials in the adjuvant setting. The use of trastuzumab as part of an adjuvant therapy in patients whose tumors overexpress HER2/*neu* should be strictly limited to the context of clinical trials

In conclusion, the international 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 cytotoxic agents became more evident. The Panel members were more than ever convinced that much more can be achieved to increase knowledge about the disease and improve patient care if

participation in clinical trials becomes more acceptable to the public as well as to the medical community. International cooperation on trials and their evaluation must lead to the investigation of critical biologic principles rather than establish the superiority of particular pharmaceuticals for regulatory purposes. A collaborative approach involving the development of new agents and investigation of their optimal integration into adjuvant therapy programs will best ensure progress for improved patient care.

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APPENDIX

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