Abstract: Primary systemic therapy (PST) represents the standard of care in patients with locally advanced breast cancer. In addition, there is increasing information on PST in operable breast disease that supports the use of PST in routine practice. However, current regimens and techniques vary. To address this concern, a group of representatives from breast cancer clinical research groups in France, Germany, Italy, the United Kingdom, and the United States reviewed all available data on prospective randomized trials in this setting. Recommendations are made regarding terminology, indications, regimen, diagnosis before treatment, monitoring of efficacy, tumor localization, surgery, pathologic evaluation, and postoperative treatment.

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tumor response to serve as an in vivo chemosensitivity test: A reduction in the primary tumor volume can be used to predict a reduction in micrometastatic tumor volume as well as clinical benefit.

Much of the evidence comparing PST with AST is from randomized controlled clinical trials in patients with operable (stage T1c-3, N0, M0 or T1–3, N1, M0) breast cancer. These studies have shown that primary (preoperative) systemic therapy with cyclophosphamide, methotrexate, and fluorouracil22; doxorubicin and cyclophosphamide (AC)23; fluorouracil, doxorubicin, and cyclophosphamide24, or fluorouracil, epirubicin, and cyclophosphamide25 offers the same disease-free survival and overall survival benefits as does AST with the same drug combinations (Table 2). In addition, PST results in an increase in the proportion of patients who are subsequently shown to have axillary lymph nodes free of metastatic involvement or who become candidates for breast-conserving surgery.

Several clinical trials in operable breast cancer have compared different PST regimens in patients with breast tumor sizes as small as 1 to 2 cm (Table 3). Complete pathologic remission (pCR) of these tumors correlates strongly with both prolonged disease-free survival and overall survival26–29 (even though tumor progression during PST is rare [approximately 3%], its occurrence predicts a poor prognosis).14,25,26 The absence of identifiable tumor cells in the removed breast tissue has been reported in 6% to 19% of patients who have received PST (Table 3).30–36 In most of the large clinical trials that compare PST with AST, the primary chemotherapy regimens that result in higher pCR rates are also associated with a higher rate of successful breast conservation and a higher proportion of patients subsequently found to have axillary lymph nodes free of metastatic involvement. None of the larger trials has detected a disease-free survival or overall survival advantage in favor of PST. One small clinical trial showed a potential advantage with the use of preoperative chemotherapy because clinical response to the first regimen was used as a guide in selecting additional therapy.29 At present, this approach has not been confirmed in a more appropriate trials setting and was not compared with conventional postoperative chemotherapy.

METHODS

In October 2001, representatives of a number of breast cancer clinical research groups from France, Germany, Italy, the United Kingdom, and the United States (see Appendix) were invited to join the panel. All representatives have been chairpersons of

Table 1. Historic Development of Primary and Adjuvant Systemic Therapy in Breast Cancer

<table>
<thead>
<tr>
<th>Decade</th>
<th>Aims of Primary Systemic Therapy</th>
<th>Aims of Adjuvant Systemic Therapy</th>
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<tbody>
<tr>
<td>1970</td>
<td>—</td>
<td>Immediately after surgery, to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>destroy disseminated tumor cells induced by mechanical manipulation</td>
</tr>
<tr>
<td>1970s</td>
<td>To achieve operability in locally advanced tumors</td>
<td>To destroy micrometastases already present before surgery (for weeks or months)</td>
</tr>
<tr>
<td>1980s</td>
<td>To improve the breast conservation rate in operable breast cancer</td>
<td>To overcome drug resistance using new compounds (anthracyclines)</td>
</tr>
<tr>
<td>1990s</td>
<td>To destroy or alter multicentric or multifocal tumor cells in the breast (resulting in fewer ipsilateral in-breast recurrences)</td>
<td>To overcome drug resistance by increasing dose-intensity</td>
</tr>
<tr>
<td>&gt; 2000</td>
<td>To select chemoresistant or sensitive tumors</td>
<td>To improve single-drug intensity by sequential application</td>
</tr>
</tbody>
</table>

Table 2. Overview of Randomized Trials Comparing Primary Systemic Therapy and Adjuvant Systemic Therapy in the Breast

<table>
<thead>
<tr>
<th>Author and Group</th>
<th>No. of Patients</th>
<th>Tumor-Node-Metastasis Classification</th>
<th>Tumor Size (cm)</th>
<th>Regimen</th>
<th>Follow-up (months)</th>
<th>Local Failure Rate</th>
<th>Distant Failure Rate</th>
<th>Survival Rate</th>
<th>Breast Conservation (PST versus AST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher,2,28 NSABP</td>
<td>1,523</td>
<td>T1-3, N0-1, M0</td>
<td>All</td>
<td>AC × 4</td>
<td>96</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>67% versus 60% P = 0.002</td>
</tr>
<tr>
<td>Gianni,26 ECTO</td>
<td>892</td>
<td>T1-3, N0-1, M0</td>
<td>≥ 2</td>
<td>AT-CMF</td>
<td>23</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>71% versus 35% P &lt; 0.0001</td>
</tr>
<tr>
<td>Van der Hage,25 EORTC</td>
<td>698</td>
<td>T1c-4d, N0-1, M0</td>
<td>≥ 1</td>
<td>FEC × 4</td>
<td>56</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>37% versus 21.1%</td>
</tr>
<tr>
<td>Jakesz,22 ABCSG</td>
<td>423</td>
<td>T1-3, N0-2, M0</td>
<td>All</td>
<td>CMF × 3†</td>
<td>NA</td>
<td>††</td>
<td>*</td>
<td>*</td>
<td>*NA</td>
</tr>
<tr>
<td>Scholl,24 S6</td>
<td>390</td>
<td>T2-3, N0-2, M0</td>
<td>3-7</td>
<td>FAC × 4</td>
<td>66</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>82% versus 77%</td>
</tr>
</tbody>
</table>

Abbreviations: PST, primary systemic therapy; AST, adjuvant systemic therapy; NSABP, National Surgical Adjuvant Breast and Bowel Project; ECTO, European Cooperative Trial on Operable Breast Cancer; EORTC, European Organization for Research and Treatment of Cancer; ABCSG, Austrian Breast Cancer Study Group; S6, Study 6; NA, not available; AC, doxorubicin and cyclophosphamide; AT, doxorubicin and paclitaxel; CMF, cyclophosphamide, methotrexate, and fluorouracil; FEC, fluorouracil, epirubicin, and cyclophosphamide; EC, epirubicin and cyclophosphamide; FAC, fluorouracil, doxorubicin, and cyclophosphamide.

*No statistical difference between study arms.
†An additional three cycles of CMF or EC given postoperatively.
‡Statistically significant increase.
trials exploring PST or members of the corresponding trials' steering committees, or are reference experts for pathology, radiodiagnostic, surgical, and radiotherapeutic points of view.

For Whom Can PST Be Recommended as an Alternative to AST.

For Whom Is PST the Standard of Care?

Existing treatment patterns, although they are not based on the results of large randomized clinical trials, indicate that PST is considered the standard treatment for patients with inoperable primary breast cancer (ie, patients with locally advanced tumors for whom it is expected that local control cannot be attained by surgical means alone). In most cases, these patients represent a group with an unfavorable prognosis (stage IIIA-B or T3–4 disease), including classic inflammatory breast cancer or involvement of ipsilateral supra- or infracavicular lymph nodes (N3). In operable breast cancer, PST can be considered as an alternative to AST.

For Whom Can PST Be Recommended as an Alternative to AST?

All large randomized clinical trials of PST versus AST indicate that these therapies offer patients equivalent disease-free survival and overall survival benefits (Table 2). PST is thus a reasonable alternative for patients with operable breast cancer.
who are deemed to be appropriate candidates for mastectomy but who desire less extensive surgery (e.g., breast-conservation surgery). PST is also increasingly used in patients who can technically have a lumpectomy first but whose physical appearance will be less damaged if PST is given first.

Numerous investigators have found that the rate of successful breast-conservation surgery is statistically significantly increased, as well as clinically relevant, in patients who receive PST compared with those who receive AST. Reported absolute differences in the rate of successful breast-conservation surgery between patients who receive PST and those who receive AST range from 5% to 36% (Table 2). The difference in the rate of successful breast-conservation surgery among patients who receive various primary systemic chemotherapy regimens ranges from 2% to 19% (Table 3).

In addition to the type of primary systemic chemotherapy, the rate of successful breast-conservation surgery also correlates with clinical response and the size of the primary tumor. Patients who experience a clinical complete response may have a successful breast-conservation rate of 90% and more.30,34 Patients who receive PST can increase their chance for breast conservation by 12.5% if the tumor size is 2 to 5 cm, and by 17.5% if the tumor size is more than 5 cm.23 In the largest trial reported to date, in which patients had a median follow-up time of 8 years, no statistically significant difference was found in local recurrence-free survival between patients treated with PST (four cycles of AC) and those treated with AST (four cycles of AC).37

The local recurrence rate among those who achieved complete clinical response was as low as 5.6%, and among those who did not achieve complete clinical response, the local recurrence rate was 9.7%. The local recurrence rate did not correlate with size of the primary tumor before treatment. However, among a small cohort of 69 patients who were considered candidates for mastectomy before receiving PST, a local recurrence rate of 14.5% was reported. This is in contrast to the 6.9% local failure rate seen among patients initially thought to be candidates for breast-conservation surgery who received PST.28 In another small trial,22 patients who did not respond to PST had a significantly increased risk of recurrence compared with those who did respond to PST.

These results are consistent with the hypothesis that a poor response to PST is a predictor of poor prognosis and a high risk of recurrence, irrespective of the type of surgery performed. The results may also indicate that patients who convert to breast-conserving surgery as a result of PST also have a higher risk of experiencing local treatment failure.

Because at present there is no evidence that PST offers a disease-free survival or overall survival benefit over AST, knowledgeable patients may choose to receive systemic therapy before surgical resection to take advantage of the response-assessment of the primary tumor before it is removed. A demonstrable response to PST may have a positive effect on the patient’s compliance with additional treatment and on the patient’s willingness to accept some adverse events. When the primary tumor increases in size during PST, immediate surgical intervention should be considered, with the aim of avoiding additional adverse effects of ineffective systemic treatment.

PST may also be advisable for certain patients who have medical contraindications to surgery or simply wish to delay surgery. For example, PST can be used in the second or third trimester in pregnant patients diagnosed with breast cancer; this is followed by surgery and radiotherapy after delivery.38

PST offers an optimal test situation for the evaluation of new compounds and the detection of new biologic or molecular discriminants of either response or resistance. pCR may be used as a surrogate end point to substitute for survival and potentially provides a possibility of avoiding the arduous process of large randomized trials. In addition, tissue banking before, during, and after PST may permit the identification of undiscovered patterns of presentation of biologic or molecular discriminants that could help exclude ineffective treatments and optimize systemic regimens (Fig 1).
How Should a Diagnosis of Invasive Breast Cancer Be Confirmed Before PST?

Core biopsy and histologic examination are considered the most appropriate techniques for the detection of both invasive and noninvasive breast carcinomas. The highest diagnostic accuracy for confirming malignant disease can be reached by obtaining at least three core biopsies from various locations within the primary tumor using, at minimum, a 14-gauge needle. In contrast to the relatively small cytologic sample obtained by fine-needle aspiration biopsy, the three ≥ 14-gauge cores obtained by core biopsy should provide enough tissue to obtain up to 5% of the patients who progress after the first regimen, an alternative approach to surgery at that point would be to proceed with a potentially non–cross-resistant second chemotherapy regimen. In this case, however, the patient must be monitored closely to avoid significant tumor progression and inoperability.

Is There a Role for Endocrine PST Alone?

Because of the lower response rates in published endocrine trials compared with response rates in chemotherapy PST trials, we cannot recommend the use of hormonal manipulation for PST as a standard of care. In the largest of such trials, which included 337 patients, a pCR was observed in only 1.5% of patients.

Nevertheless, endocrine therapy remains attractive for patients for whom it is desirable to avoid certain chemotherapy-related adverse events. Clinical trials that evaluate endocrine PST or short-course presurgical endocrine PST in patients with hormone receptor–positive tumors may help answer questions about the endocrine-induced modulation of biologic markers.

Endocrine therapy may be considered a second choice for selected patients; for example, for elderly women with impaired organ function, for patients who are unwilling to accept the adverse events associated with chemotherapy, for those with a low performance status, or for those who are at increased surgical risk. A positive ER or PgR status (or both) is a prerequisite for this treatment approach because hormone receptor content is predictive of the efficacy of endocrine compounds. According to prospective data from one randomized PST trial and several sequential phase II studies, aromatase inhibitors are more active and better tolerated than tamoxifen and thus are preferred in postmenopausal patients. At present, there are no data available about the efficacy of endocrine PST in premenopausal patients.

Which Regimen Is Recommended for PST?

There is sufficient evidence to justify the use of anthracycline-based chemotherapy regimens outside clinical trials. A minimum of three or four cycles should be given, and additional cycles may be considered for responding patients to maximize response and to improve the probability of successful breast-conservation surgery in patients with otherwise nonoperable breast cancer. As in the adjuvant setting, in which four cycles of AC are currently widely considered to be inferior treatment for women with positive nodes, there is increasing evidence that the additional use of taxanes or the use of sequential therapies as PST in operable breast cancer is superior. Both can increase the rate of clinical and pCR of the primary tumor, the proportion of patients who have successful breast-conservation surgery, and the number of patients found to have axillary nodes not involved with tumor cells (Table 3). However, to date, as noted above, only one small trial shows potential advantage for overall survival with sequential, non–cross-resistant regimens of PST. It is also now evident that if patients do not experience a response after three or four cycles of systemic chemotherapy, they are less likely to respond to alternative chemotherapy regimens delivered as second-line PST. This group of patients should be offered immediate surgical resection. However, because clinical responses have been observed with the second-line PST in up to 50% of the patients who progress after the first regimen, an alternative approach to surgery at that point would be to proceed with a potentially non–cross-resistant second chemotherapy regimen. In this case, however, the patient must be monitored closely to avoid significant tumor progression and inoperability.

Trastuzumab and other new targeted therapies are still under investigation and should not be used outside clinical trials.

How Should Chemotherapy and Endocrine Treatment Combinations Be Administered?

Endocrine treatment should be added to chemotherapy according to the standard recommendations for the adjuvant therapy of breast cancer. All patients with ER-positive or PgR-positive tumors (or both) are candidates for adjuvant endocrine treatment. Recently, it has been demonstrated that the sequential use of tamoxifen after the end of cyclophosphamide, doxorubicin, and fluorouracil chemotherapy leads to a longer disease-free survival than simultaneous use. This is in concordance with results showing that the concurrent use of chemotherapy and tamoxifen in PST increases toxicity without a demonstrable improvement in benefit. Sequential treatment (ie, starting endocrine treat-
ment after surgery and completion of chemotherapy) is therefore recommended.

How, When, and How Often Should the Effect of PST Be Monitored?

The present standard of care is to carry out palpation of the primary tumor and regional lymph nodes before the start of chemotherapy and at the end of each cycle. Mammography or breast ultrasonography (or both) is optional, but either technique may be useful when the clinical response is ambiguous or to confirm progression. However, it is important to emphasize that this requires a baseline examination using the same technique (mammography or ultrasound) before PST is begun. Additional methods, such as magnetic resonance imaging or positron emission tomography of the breast, should only be used in the context of clinical trials.

Possible definitions used to report tumor response to primary systemic treatment are given in Table 4.

How Should Tumor Location Be Documented?

PST requires collaboration among the medical oncologist, cancer surgeon, and diagnostic radiologist. All three disciplines should be involved in treatment decision making and in patient follow-up during PST. Cooperation is particularly important if the patient’s tumor does not respond to PST and immediate surgery is required. Close interdisciplinary patient follow-up is also required should the tumor shrink rapidly and presurgical tumor localization become difficult.

The radiation oncologist will play an important role in deciding if postoperative radiation therapy is indicated and in its planning. Preoperative external beam and brachytherapy are not established as modes of treatment in conjunction with PST. For this reason, precise documentation of the tumor location with a sketch (Fig 2) or photographs (or both) is strongly recommended. Such documentation can provide the surgeon with sufficient information to locate the tumor bed in case of complete tumor remission, and to estimate the initial tumor size in case of tumor shrinkage. Different marking procedures have been recommended in clinical trials (eg, inserting clips or coils in the center of the lesion or placing a tattoo on the skin; stereotactic location of the initial tumor area using mammography, guided by the baseline film, is also feasible. The complete disappearance of the tumor on clinical examination or by mammography or breast ultrasound has been a rare event until recently, but with the increasing rate of pCR, this may become more frequent, and standardized location procedures need to be developed.

How Should the Tumor Be Treated Surgically?

The aim of surgery with or without PST is to obtain clear margins of at least 1 mm at pathology examination; tumor-free margins after the use of PST should be ≥ 1 mm. It is assumed that defined tumor-free margins will result in a higher breast conservation rate. No compromise should be made in surgical margins to obtain a better cosmetic result.

Again, no significant difference has been found between PST and AST in 8-year local recurrence rates of breast cancer (randomized trials).37 Patients diagnosed before the age of 40 years and those with larger tumors, high rates of tumor proliferation, or close or involved surgical margins are at higher risk for ipsilateral tumor recurrence after breast-conserving surgery.44 This may be due to the aggressive characteristics of the primary tumor, to suboptimal surgery, or to the increased difficulty a surgeon may have when estimating tumor area after multifocal tumor shrinkage induced by PST occurs.30 For these women, an increased rate of second surgical procedures has been reported.35 Patients should be informed about this possible disadvantage before deciding for or against the use of PST.

How Should Tumor Tissue Be Examined by the Pathologist?

The pathologist can only provide an appropriate examination of the surgical specimen if he or she has been informed about whether PST was used. We recommend systematic sectioning perpendicular to the long axis of the specimen; random sections or a so-called orange-peel technique is not

<table>
<thead>
<tr>
<th>Table 4. Definitions for Response Evaluation of Primary Systemic Therapy in Breast Cancer</th>
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<tbody>
<tr>
<td>Clinical definition</td>
</tr>
<tr>
<td>Partial: reduction of tumor area to ≤ 50% (cPR)</td>
</tr>
<tr>
<td>Complete: no palpable mass detectable (cCR)</td>
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adequate. X-rays of the specimen may help detect tumor foci not otherwise apparent. A detailed report should be given that includes the extent of the primary tumor, the presence or absence of multifocality, the extent of an intraductal component, the presence of lymphatic tumor emboli, host response, and lymph node response.

We advise that the summary report should include a reference to one of the recognized grading systems for tumor regression. The presence or absence of invasive or noninvasive tumor components should be clearly stated (Table 4). Posttreatment pathology assessment of the tumor should be completed using the tumor-node-metastasis staging system.

What Is the Role of Postoperative Chemotherapy After PST?

For patients with inflammatory breast cancer, it has been argued that postoperative chemotherapy is an integral part of treatment, but it is more appropriate to administer maximum chemotherapy before surgery, when its efficacy can be easily assessed. To date, there are no data that support or negate the use of postoperative chemotherapy when the response of the primary tumor or regional lymph nodes to PST is inadequate. It is not known whether the use of preoperative and postoperative chemotherapy together provide better or worse results than the results obtained from administration of all chemotherapy preoperatively.

Conclusive data on this point may become available in the near future from the National Surgical Adjuvant Breast and Bowel Project Trial B-27 or from the European Cooperative Trial in Operable Breast Cancer.

When and Where Should Postoperative Radiotherapy Be Administered?

Whereas radiotherapy is considered a standard part of the treatment regimen for patients with locally advanced breast cancer, in operable breast cancer, radiotherapy after PST should be administered according to the same recommendations made for those who do not receive PST. An indication for postmastectomy radiotherapy of the chest wall (with or without regional lymph nodes) on the basis of tumor size should be based on initial tumor size. The unfavorable prognosis associated with axillary lymph nodes shown to be involved with tumors after the completion of PST should also be taken into account. Even in patients who experience histologically complete remission, whole-breast irradiation is indicated after breast-conserving surgery. There are no definitive data on the importance of nodal status after PST and the need for axillary radiotherapy. Treatment decisions in these situations must be made on an individual basis. Although preoperative radiotherapy improves the rate of successful breast-conservation surgery and is feasible without compromising cosmetics, there are sufficient data to demonstrate that radiotherapy is not a substitute for surgery; locoregional control is inadequate when the patient is treated with radiotherapy alone.

What Issues Remain to Be Resolved?

The use of preoperative PST, with the aim of improving operability, rather than postoperative systemic therapy is only the first step in exploring the advantages of primary (preoperative) treatment. Future research should concentrate on the way in which PST, acting as an in vivo chemosensitivity test, can be used to benefit each patient. The selection of patients for a specific treatment that offers them a high probability of achieving pCR is crucial, and PST is an ideal tool with which to assess predictive clinical and pathologic factors. Examining tumor tissue before, during, and after PST is possible using modern technology such as immunohistochemistry, fluorescence in situ hybridization, DNA microarrays, tissue microarrays, or proteomics (Fig 1).

New compounds directed against specific molecular targets associated with the tumor should be explored in the primary therapy setting. The use of such compounds for PST may demonstrate their effect and proof of concept that the target may serve as a surrogate marker for either clinical benefit or disadvantage, which could lead to the development of new drugs that have demonstrated activity against breast cancer.

PST is considered the standard of care for nonoperable, locally advanced breast cancer. For operable breast cancer, PST provides additional opportunity for breast-conserving surgery. Current data indicate that pCR may be used as a surrogate indicator for the beneficial effect of PST on both disease-free and overall survival. On the basis of the biologic characteristics of a tumor and differences in the response to systemic treatment, PST should be regarded as a tool that can be used to individualize systemic therapy for patients with breast cancer.

ACKNOWLEDGMENT

This manuscript is written in memory of Helen Louise Smith. The authors thank Barbara C. Good, PhD, for editorial assistance, and Theodor Weigel, BANSS-Foundation, for financial support.

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.

REFERENCES


