Guidelines for International Breast Health and Cancer Control–Implementation

Supplement to ***Cancer***

Locally Advanced Breast Cancer

Treatment Guideline Implementation With Particular Attention to Low- and Middle-Income Countries

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The management of locally advanced breast cancer (LABC) is guided by scientific advances but is limited by local resources and expertise. LABC remains very common in low-resource countries. The Systemic Therapy Focus Group met as part of the Breast Health Global Initiative (BHGI) Summit in Budapest, Hungary, in October 2007 to discuss management and implementation of primary systemic therapy (PST) for LABC. PST is standard treatment for large operable breast cancer in enhanced-resource settings and, in all resource settings, should be standard treatment for inoperable breast cancer and for LABC. Standard PST includes anthracycline-based chemotherapy. The addition of sequential taxanes after anthracycline improves pathologic responses and breast-conservation rates and is appropriate at enhanced-resource levels; however, costs and lack of clear survival benefit do not justify their use at limited-resource levels. It remains to define better the role of endocrine therapy as PST, but it is acceptable in elderly women. Aromatase inhibitors have produced better results than tamoxifen in postmenopausal patients and are used in enhanced-resource settings. The less expensive tamoxifen remains useful in low-resource countries. Trastuzumab combined with chemotherapy yields high pathologic response rates in patients with HER2/*neu*-overexpressing tumors; its use in low-resource countries is limited by high costs. Most studies on PST of LABC were conducted in countries with enhanced resources. BHGI encourages conducting clinical trials in countries with limited resources. ***Cancer*** **2008;113(8 suppl):2315–24.** © *2008 American Cancer Society.*

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Systemic therapy for breast cancer incorporates chemotherapy, targeted therapy, and hormone manipulation. It is used for metastatic disease, as postoperative adjuvant therapy for primary breast cancer, and as neoadjuvant (preoperative) therapy for locally advanced breast cancer (LABC). Systemic therapy is driven by scientific evidence; however, its implementation is subject to available

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expertise and local resources.[1] Treatment involves the use of a wide range of medications from inexpensively priced tamoxifen to expensive, targeted therapy agents, such as trastuzumab and lapatinib.

Neoadjuvant therapy also is called primary systemic therapy (PST) or preoperative therapy and has been studied widely for the treatment of LABC and primary operable breast cancer.[2] PST usually is followed by locoregional therapy. Although the incidence of LABC has decreased significantly in countries with enhanced resources thanks to widespread education and screening programs,[3-5] it remains a daily encounter for surgeons and oncologists in low-resource countries. LABC and metastatic breast cancer are the most common stages at presentation in most low-resource countries.[6-9] LABC represents a daily challenge for management and resource allocation and for early diagnosis.

This article addresses the management and implementation of PST for LABC, as discussed by a Systemic Therapy Focus Group (the Focus Group) that met as part of the Breast Health Global Initiative (BHGI) conference in Budapest, Hungary, in October 2007. Levels of resources are outlined in the overview in this supplement to *Cancer* and in previous publications.[10]

Definitions, Diagnosis, and Staging of Locally Advanced Breast Cancer

LABC is a heterogeneous clinical entity that includes patients with large (>5 cm) primary breast tumors or T4 tumors with chest wall involvement, skin edema, including peau d'orange or ulceration of the skin; satellite nodules; confined to the same breast; or inflammatory carcinoma and/or extensive clinical lymph node involvement, as defined by the N2 and N3 categories from the American Joint Committee on Cancer TNM classification system (see Table 1).[11,12]

All patients need to have adequate tissue diagnosis and staging. The initial management of LABC requires histologic sampling (eg, core biopsy, incisional biopsy) for confirmation of the diagnosis and for determination of hormone receptor status before the initiation of neoadjuvant therapy. Although core biopsy is preferred in countries with enhanced and maximal resources, it is used to a lesser extent in low-resource countries because of cost and limited availability of radiologic and pathologic services.[13] The availability of resources to provide accurate histologic diagnosis and accurate assessment of prognostic and predictive factors, such as the presence or absence of estrogen receptors (ER) and progesterone receptors (PR) in a tumor, is crucial for making decisions regarding systemic therapy and for providing cost-effective breast cancer care. Fine-needle aspiration biopsy (FNAB) is a simpler procedure that is less expensive and requires less equipment and material than core biopsy. It reduces the waiting time for diagnosis at much lower costs. The Focus Group agreed that FNAB remains an important diagnostic modality and may be sufficient to yield a diagnosis of malignancy, particularly in cases of suspected malignancy, by using clinical and/or radiologic features. FNAB cannot differentiate invasive cancer from noninvasive cancer, although a positive FNAB of a regional lymphadenopathy confirms regional metastases and, by inference, invasive breast cancer.

TABLE 1
Locally Advanced Breast Cancer Definitions

LABC that may be operable at presentation
Stage IIIA: T3 with any N; N2 with any T1–T3
LABC that is inoperable at presentation
Stage IIIB: T4a, skin; T4b, chest wall; T4c (a+b)
Stage IIIC: N3 with any T
T4d (inflammatory breast cancer)

LABC indicates locally advanced breast cancer.

The Focus Group discussed extensively the issues related to hormone and HER2 receptor determination and the impact of these markers on treatment decisions. The Focus Group considers core biopsy important for determining pathology and receptor status before neoadjuvant PST. Core biopsy provides sufficient tissue for the determination of receptor status when PST is planned; however, a well prepared cell block from FNAB and a trained cytopathology team may be adequate to assay for receptors. Core biopsy generally is done under ultrasound guidance; however, in patients with LABC, it can easily be guided by manual palpation and can provide sufficient tissue for receptor determination. Staging must include a complete history and physical examination. It should also include basic tests like complete blood counts, liver function tests, alkaline phosphatase levels, and calcium levels. Minimal workup also includes a chest x-ray, ultrasound of the abdomen, and a bone scan, if available.[14,15] In countries with enhanced and maximal resources, bilateral mammography and bone scan, as well as chest and abdominal computed tomography scans are recommended for LABC.

Management of Locally Advanced Breast Cancer

In this report, we review the available literature and discuss the implementation of multidisciplinary therapy according to the availability of resources,

especially for countries with limited and/or basic resources. Patients with T3 lesions may undergo primary surgical resection but generally are offered PST in countries with enhanced and maximal resources. A recent review of published data indicates that a large number of patients may be converted from modified radical mastectomy (MRM) to breast-conserving surgery (BCS) by neoadjuvant therapy.[16] The initial treatment approach may differ according to the available expertise and the level of resources. In countries with limited and basic resources, where pathology is not readily accessible and where no optimal chemotherapy is available, surgery remains the primary treatment approach for patients with T3 tumors.

Primary Systemic Therapy for Locally Advanced Breast Cancer: Role and Type of Chemotherapy

Major individual trials and a meta-analysis, which was published in 2005, have assessed response and benefit of PST and have helped to identify factors that are predictive of response, recurrence, and effect on survival.[17-30] Those trials included patients who had large primary tumors and patients who had T2 tumors. The Focus Group noted that all major studies and clinical trials that were available for analysis were conducted in countries with enhanced or maximal resources. No trials were available from countries with limited or basic-level resources. Here, we review and analyze those results and emphasize the aspects related to large and locally advanced tumors along with as issues related to low-resource countries.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 study tested 4 cycles of combined doxorubicin and cyclophosphamide (AC) followed by surgery versus surgery followed by AC. The results established that preoperative AC chemotherapy does not harm patients and is at least as effective as postoperative adjuvant therapy.[19] The NSABP B-27 study tested the addition of docetaxel to AC, either preoperatively or postoperatively.[27] The Aberdeen trial (TAX 301) tested preoperative docetaxel after the administration of combined cyclophosphamide, vincristine, doxorubicin, and prednisone as neoadjuvant therapy.[22] Those trials produced concordant results regarding improved breast-conservation rates and higher pathologic complete response (pCR) rates with the addition of preoperative docetaxel. A benefit also was noted from using alternating noncross-resistant regimens in the smaller TAX 301 study. Better survival was reported in responders, but the overall effects on survival were conflicting. Those trials mostly were underpowered to determine the survival effect of modest improvements in the pCR rate. A very recent update of the NSABP B-18 trial continued to demonstrate no statistically significant differences in disease-free survival (DFS) or overall survival between the preoperative and postoperative groups. The addition of docetaxel to AC in the B-27 Protocol study increased significantly the proportion of patients who had a pCR (26% vs 13%,). After 16 years of follow-up, the patients in that study who achieved a pCR continued to have superior DFS and overall survival outcomes compared patients who did not achieve a pCR.[31]

A meta-analysis of 9 randomized clinical trials with a total of 3946 patients also is included in the current review. The authors of that report noted that pCR rates were highly variable among the 9 trials. Six trials had a higher rate of BCS after PST. The meta-analysis also reported large variability and heterogeneity in the range of response rates reported in the analyzed trials (clinical CR rate, 7%-65% pCR rate, 4%-29%). The rates of choosing conservative surgery also ranged between 28% and 89%. No differences were observed between the 2 arms for death, disease progression, or distant recurrence. The meta-analysis also revealed that patients who received PST and underwent BCS had an increased risk of locoregional recurrence, especially those who received radiation therapy without surgery.[28] Radiation therapy without surgery, even in the presence of a good clinical response to PST, should be avoided.[29] Surgery remains an essential part of the management of early breast cancer, and it is important to note that there is an increased local failure rate in those patients who require chemotherapy to undergo breast conservation.[30] In the absence of a demonstrated survival benefit, it may be important to note that the sample size of the B-27 study was not sufficient to yield significance for the moderate DFS improvement; the concurrent use of tamoxifen may have limited the impact of chemotherapy.[27] We now know from Intergroup Trial 0100 that concurrent tamoxifen reduces the effects of chemotherapy by 50%[32] It also is noteworthy that there was a marginal survival benefit in the NSABP B-18 study in the preoperative arm for younger patients[19]; this may turn out to be important in low-resource countries, where there are greater percentages of young women with breast cancer.[7]

Evaluation of the response to chemotherapy and margins of resection is an essential part of management. Residual disease after PST does appear to have an important impact on survival. In the M. D. Anderson Cancer Center trial,[27,33] patients who had residual tumors >1 cm had less favorable outcomes. A

recent 8-year update of B-18 and B-27 at a special National Cancer Institute meeting on PST[31] noted that a high rate of locoregional recurrence was predictable by tumor size >5 cm and by the presence of positive lymph nodes either at presentation or after PST. This is a relevant issue that emphasizes the importance of optimal pathologic evaluation of response to PST. Those issues also are very important when PST is applied in countries with limited resource. The use of PST should include a clear preoperative workup, adequate pathologic evaluation of margins at the time of surgery, the ready availability of radiation oncology, and long-term follow-up. Patients should be assured that any recurrence will be diagnosed early and treated promptly.

Patients who are treated with neoadjuvant chemotherapy need to be monitored carefully for evidence of response. Patients with LABC who have tumors that respond to primary chemotherapy fare better than those who have nonresponding tumors. Achieving a pCR to primary chemotherapy predicts better survival, as noted above. Patients with responding tumors should receive neoadjuvant treatment for up to 8 cycles, depending on the response of disease and the chemotherapy regimen used; the threshold for anthracycline-associated cardiac toxicity should not be exceeded. Patients who do not respond after 4 cycles of optimally dosed anthracyclines generally should receive local treatment.

With regard to the choice of therapy, the Focus Group agreed that, in patients who have large, operable tumors, PST should be the preferable primary therapy, because it allows an early assessment of sensitivity to treatment as well as breast conservation. However, if optimal chemotherapy and evaluation are not available, then primary MRM is acceptable. Patients with inoperable, locally advanced stage tumors should receive PST, which includes an anthracycline-based regimen. There is enough evidence of benefit from anthracycline combination to recommend it as a standard part of systemic therapy combinations for LABC. In addition, there is a large amount of literature indicating an added benefit when taxanes are included, particularly when they are sequenced with anthracycline combinations.[22,27,29,34-37] New data support weekly paclitaxel as better than 3-weekly, although 3-weekly dosing for docetaxel remains standard.[38,39] The NSABP B-27 Trial included patients with T3 tumors and demonstrated that the addition of sequential docetaxel in PST improved clinical CR rates from 40% to 65% and improved pCR rates from 13.7% to 26.1%. The rate of negative axillary lymph nodes also improved from 51.5% to 59.5%.[26] In the TAX 301 Aberdeen Trial of patients with LABC, all had tumors >3 cm. Docetaxel (Taxotere) improved the BCS rate from 48% to 67%.[22] Support for the role of taxanes also came from a recent report of 426 patients who received neoadjuvant therapy from 1974 to 2001 at the M. D. Anderson Cancer Center.[34,39] All 426 patients were given taxane-based PST. In that report, the pCR rate in patients with ER-negative tumors was 20.1%, whereas the pCR rate in patients with ER-positive tumors was 4.9%. In the patients with ER-negative tumors, the pCR rate was 29% when a taxane was used, but it was only 15% without a taxane. Conversely, in the patients with ER-positive tumors, the pCR rate was 8.8% when a taxane was used and only 2% without a taxane. The authors reported that, in multivariate analysis, there was an independent association between the pCR rate and clinical tumor size, ER-negative status, and inclusion of a taxane in the chemotherapy regimen (for a summary, see Table 2).

TABLE 2
Primary Systemic Therapy in Locally Advanced Breast Cancer: Neoadjuvant Chemotherapy Summary

Primary systemic chemotherapy is standard of care at all levels of resources
Primary surgery is an acceptable alternative in patients with operable stage IIIA disease if BCS is not available in low-resource settings
PST downstages tumors, makes them operable (MRM or even BCS in some situations)
PST treats micrometastases upfront
Results of presurgical chemotherapy are equivalent to postsurgical chemotherapy
PST up to 31% of patients achieve pCR: Patients with pCR have better DFS and OS
Multidisciplinary management is mandatory: A small core team of a surgeon, radiologist, pathologist, oncologist, and a nurse may be enough in limited-resource countries; a full team in higher resource settings
PST provides opportunity to study sensitivity and biology of tumors to chemotherapeutic agents: This may be a great window of opportunity to study the particularities of LABC in young women and triple-negative tumors in low-resource countries

BCS indicates breast-conserving surgery; PST, primary systemic therapy; MRM, modified radical mastectomy; pCR, pathologic complete remission; DFS, disease-free survival; OS, overall survival; LABC, locally advanced breast cancer.

New Role for Trastuzumab in Primary Systemic Therapy

The introduction of the anti-HER2/*neu* receptor monoclonal antibody trastuzumab is one of the most important recent advances in breast cancer therapy. Trastuzumab has found a place in the treatment of HER2-amplified metastatic disease and as adjuvant therapy for primary breast cancer, and now it is incorporated into PST regimens for patients with HER2-positive LABC.[40-43] A randomized phase 3 trial[40] compared a 6-month course of preoperative

TABLE 3
Primary Systemic Therapy in Locally Advanced Breast Cancer: Neoadjuvant Biologic Targeted Therapy

HER2-overexpressing tumors
Trastuzumab used in combination with sequential taxane and anthracycline combinations: Trastuzumab raises pCR rate up to 67%
Long-term results and toxicities of neoadjuvant trastuzumab are awaited
Lapatinib has been incorporated into new clinical trials
Targeted therapy applied in countries with enhanced and maximal resources
Expenses remain prohibitive and does not allow use in low-resource countries
HER2-nonoverexpressing tumors
Targeted antiangiogenic therapy, in combination with systemic chemotherapy, is undergoing clinical investigation in enhanced/maximal resource settings

pCR indicates pathologic complete remission.

TABLE 4
Primary Systemic Therapy in Locally Advanced Breast Cancer: Neoadjuvant Hormone Therapy

Tamoxifen produces variable clinical response rates
Tamoxifen allows breast conservation rates in up to 35% of patients
AIs produce more clinical responses than tamoxifen, up to 55%
AI allows more breast-conserving surgery than tamoxifen: up to 45% of patients
Role and duration of preoperative hormone therapy remains undefined
Hormone therapy may be justified as PST in elderly patients with known positive hormone receptors and slow-growing tumors with unknown receptor status
Tamoxifen may be justified in those situations in low-resource settings. AIs are more effective and are used in enhanced- and maximal-resource settings
Hormone therapy rarely produces complete pathologic remissions
There are no data to justify neoadjuvant hormone therapy in inoperable LABC, and chemotherapy should remain first choice
Hormone therapy should be given after surgery for hormone-responsive tumors in accordance with adjuvant therapy recommendations and durations at all levels of resources

AIs indicate aromatase inhibitors; PST, primary systemic therapy; LABC, locally advanced breast cancer.

chemotherapy, which consisted of paclitaxel for 4 cycles; followed by combined 5-fluorouracil, epirubicin, and cyclophosphamide for 4 cycles; and the same chemotherapy regimen administered simultaneously with weekly trastuzumab for 24 weeks. That trial included patients with noninflammatory, stage II and IIIA, HER2-positive breast cancer. The study was closed early after the accrual of only 42 of the 164 planned patients because of a highly significant difference in the pCR rate favoring the trastuzumab group.[41] Trastuzumab dos not need to be interrupted in the perioperative period and can be administered safely during radiation therapy.[44]

Primary Systemic Therapy for Locally Advanced Breast Cancer: The Role of Hormone Therapy

LABC has been treated with antiestrogen therapy or by the removal of sources of estrogen production, either by ovarian suppression or ovarian ablation in premenopausal women or by the use of aromatase inhibitors (AIs) in postmenopausal women.[45-50] A French study at the Bergonie Institute in Bordeaux[45] demonstrated that neoadjuvant hormone therapy is feasible and useful. That study included patients who were treated from 1984 to 1996 at a single institution. In total, 199 postmenopausal women were given first-line tamoxifen. Ninety-seven patients had operable disease (T2 tumors >30 mm, T3 tumors, N0/N1 lymph node status), and 102 patients had T4 tumors. The mean treatment duration was 5.3 months. A breast-conservation rate of 53% was noted for patients with T2 and T3 tumors, and the rate for patients with T4 tumors was 44%. Many phase 2 studies have demonstrated that tamoxifen produces clinical response rates that range between 37% and 81%.[51] Data on tamoxifen also were extracted from randomized studies that used it in a control arm and compared it with AIs, as noted below.

Letrozole was compared with tamoxifen in a randomized trial in 324 postmenopausal patients. The duration of preoperative therapy in that tamoxifen versus letrozole study (P024) was 4 months.[46] None of the 324 patients were candidates for BCS, and 14% had inoperable disease. In that study, 170 patients were randomized to receive tamoxifen, and 154 patients were randomized to receive letrozole. The response rates were 41% with tamoxifen and 60% with letrozole. The BCS rate was 36% with tamoxifen and 48% with letrozole. It is noteworthy that the response rate was significantly higher with letrozole in patients who had C-erbB-positive tumors (21% for tamoxifen compared with 88% for letrozole).[46]

In another study, 337 patients were randomized to receive either tamoxifen (175 patients) or letrozole (162 patients).[47] That study produced a better response rate (36% vs 55%) and a better breast-conservation rate (35% vs 45%) in favor of letrozole compared with tamoxifen.

Results extracted from randomized data comparing tamoxifen with AIs in postmenopausal women indicated that response rates ranged from 36% to 41% for tamoxifen and that breast-conservation rates were approximately 35%.[46-51] Higher BCS rates were noted at 44% of patients with T4 lesions in the French study described above[45] (for a summary of hormone therapy, see Tables 3 and 4).

Therefore, we conclude that, in postmenopausal women, AIs produce better response rates than tamoxifen and are recommended in countries with enhanced and maximal resources. However, in low-resource countries, tamoxifen still is useful, because it produced reasonable response rates between 36% and 41% in the studies noted above. In women with inoperable LABC who have negative or unknown receptor status for whom PST is indicated, chemotherapy should be the first choice. In elderly patients who have tumors that are slow-growing, well differentiated, and probably hormone receptor-positive, tamoxifen is justified, even if the receptor status is unknown. For premenopausal women, ovarian ablation by surgery or irradiation remains a viable option in low-resource countries; ovarian suppression with lutenizing hormone-releasing hormone (LHRH) analogs may be given to patients in countries with enhanced and maximal resources. The cost of LHRH analogs does not justify their use in countries with limited resources.

The Focus Group noted that the great majority of data regarding PST were obtained with chemotherapy, and the role of primary endocrine therapy remains to be determined. Data indicate that primary endocrine therapy is feasible and is certainly an acceptable approach for elderly women with ER-positive breast cancer. However, ER-positive LABCs in most women are treated optimally with both chemotherapy (preoperatively) and endocrine therapy (postoperatively) in a sequential fashion; and, in that context, the role of primary endocrine therapy still is undefined. Similarly, we still do not know whether any patient with LABC can be treated optimally with endocrine therapy alone.

Surgery

After an initial course of neoadjuvant chemotherapy, the use of surgery is appropriate. Most patients with LABC will require an MRM, a procedure that remains the standard surgical treatment for operable, locally advanced disease. The role of BCS in LABC is evolving and is the subject of ongoing research.

Postsurgical Radiation Therapy for Locally Advanced Breast Cancer

Patients with LABC, whether they undergo BCS or MRM, should be referred for radiation therapy.[52]

Adjuvant Therapy After the Completion of Primary Systemic Therapy and Surgery

Pathology review of the mastectomy specimen and axillary lymph nodes may reveal the complete or partial regression of breast cancer. The amount of persistent disease affects patient prognosis, and the optimal management for patients with residual disease after PST remains to be defined.[53] Although trastuzumab therapy is recommended for 1 year, and hormone therapy is recommended for at least 5 years, there are no data on additional chemotherapy. The Focus Group recommends clinical trials to address this issue should be encouraged, especially in low-resource countries where more aggressive and more advanced disease in the breast and the axilla has been described. Such studies also will help to determine the biology of aggressive tumors observed in low-resource countries. Long-term follow-up is essential because of the higher rates of local recurrence, especially in patients who require chemotherapy to undergo BCS.[28]

Multidisciplinary Management for Locally Advanced Breast Cancer

Multidisciplinary teams for the management of breast cancer in general, and LABC in particular, are strongly recommended and should be available wherever breast cancer patients are treated.[54] Even if all members of a full team of oncologist, radiologist, radiotherapist, pathologist, gynecologist, nurse, psychoanalyst, and physiotherapist are not available, all who are available should meet and discuss patient management together. In low-resource countries, the team might include only 2 to 4 members (a surgeon, radiologist, pathologist, and medical and/or radiation oncologist). Every effort should be made to have local pathologists available. It is imperative that physicians who treat patients in countries with limited resources work together and set up basic multidisciplinary teams. Patient advocates can play an important role in encouraging the setup of multidisciplinary teams, as demonstrated by the experience from Kenya presented at the BHGI 2007 Summit.[55] Health authorities are urged to issue regulations and incentives to encourage and enforce the setup of multidisciplinary teams in hospitals that treat breast cancer patients.

Primary Systemic Therapy for Locally Advanced Breast Cancer: Costs of Systemic Therapy

The implementation of scientific evidence-driven recommendations is limited by resources, the availability of manpower and modern equipment, and the costs of drugs. Cancer drugs are a major part of pharmaceutical development and profits. Noting that, among other successes, the breast cancer medication, paclitaxel (Taxol), is the highest selling drug in cancer history, pharmaceutical companies are asked to avoid overpricing medications and to reduce excessive pharmaceutical expenditures that translate

into higher drug prices.[56] It is noteworthy that the prices for chemotherapy combinations like AC, cyclophosphamide/methotrexate/fluorouracil, and cyclophosphamide/doxorubicin/fluorouracil are affordable, and those drugs are on the World Health Organization's list of essential chemotherapeutic drugs.[57] Other drugs, such as the taxanes, are expected to become less expensive in the near future, because patents are projected to expire soon.[58] Although many generics are becoming available on the international market, although the prices of some generics may rise as patents expire. The Focus Group urges international agencies and authorities to issue regulations for licensing and producing generics; to assure quality, bioequivalence, effectiveness, and low prices for generic medications; and to avoid surges when drug patents expires.[59] Patients with cancer who live in countries with limited resources have the right to have their medications controlled for quality. Countries with limited resources need technical and regulatory assistance from international organizations to control generics, copies, and counterfeit medicines.

Monoclonal antibodies and other targeted agents, including trastuzumab, have prices that are currently far beyond the resources of low-resource countries and are becoming a significant burden even for countries with enhanced resources. Cancer drug expenditures worldwide are rising significantly.[50] Monoclonal antibodies are used for long durations, which increases their costs, and they are not readily accessible to patients worldwide. These issues should be addressed with high priorities to be able to provide curative drugs for the majority of women who need them. The Focus Group discussed the possibility of administering adjuvant trastuzumab for shorter durations as per FinI Ier and ongoing studies in the United States, France, and other countries.[60,62] Physicians practicing in countries with limited resources should be encouraged to participate in such clinical trials.

Conclusions

LABC remains a daily encounter and challenge for medical and surgical oncologists in developing low-resource countries. Although operable, large tumors are managed by PST at the enhanced and maximal resource levels, they should be managed with primary surgery followed by adjuvant therapy and radiation in countries with basic resources. PST is recommended for inoperable LABC at all resource levels. PST includes anthracycline-based chemotherapy, preferably sequenced with taxanes.

Tamoxifen remains useful and is recommended for patients with ER-positive tumors in limited-resource countries. AIs produce better results than tamoxifen and are recommended for countries with enhanced and maximal resources. Chemotherapy generally is completed before surgery, and there are no data yet to support additional chemotherapy after surgery. Hormone therapy should be used after surgery for at least 5 years. Trastuzumab combined with taxanes yields high pathologic response rates in patients with HER-2/*neu*-overexpressing tumors, it is recommended in countries with enhanced and maximal resources, and it should be made available in countries with lower levels of resources at lower costs. In patients who are candidates for it, trastuzumab should be continued for a total of 1 year. Clinical trials to evaluate the role of shorter durations of trastuzumab are appropriate for countries with limited resources and should be encouraged. Most studies on PST for LABC were conducted in countries with enhanced and maximal resources. The Focus Group encourages conducting studies in countries with limited resources. Clinical trials also would provide an opportunity to study the biology and response of breast cancers encountered in low-resource countries, which, in many instances, are believed to have a different and more aggressive biologic behavior than that observed among the breast cancers in industrialized nations. The Focus Group notes that, to use PST, countries should have FNAB or breast biopsy and receptor determination available at presentation, and an adequate pathologic evaluation of response to therapy should be available.[54] To save costs, determination of ER status without progesterone receptor status is considered adequate. HER-2/*neu* receptor status is highly desirable; however, the costs of testing and subsequently trastuzumab therapy in HER-2/*neu*-positive patients remain prohibitive. Efforts should be made to make immunohistochemistry available to detect tumors with 3+ HER-2 expression and to offer trastuzumab accordingly. Tumors with 2+ HER-2/*neu* expression determined by immunohistochemistry require fluorescence in situ hybridization for confirmation, and that complementary assay is recommended at least for countries with enhanced and maximal resources. A multidisciplinary approach is imperative for the optimal management of LABC and should be developed, with whatever specialists are available, for all patients with LABC in all countries with different levels of resources.

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