Treatment of Breast Cancer in Countries with Limited Resources

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■ **Abstract:** Early and accurate diagnosis of breast cancer is important for optimizing treatment. Local treatment of early stage breast cancer involves either mastectomy or breast-conserving surgery followed by whole-breast irradiation. The pathologic and biologic properties of a woman's breast cancer may be used to estimate her probability for recurrence of and death from breast cancer, as well as the magnitude of benefit she is likely to receive from adjuvant endocrine therapy or cytotoxic chemotherapy. Ovarian ablation or suppression with or without tamoxifen is an effective endocrine therapy in the adjuvant treatment of breast cancer in premenopausal women with estrogen receptor (ER)-positive or ER-unknown breast cancer. In postmenopausal women with ER- and/or progesterone receptor (PR)-positive or PR-unknown breast cancer, the use of tamoxifen or anastrozole is effective adjuvant endocrine therapy. The benefit of tamoxifen is additive to that of chemotherapy. Cytotoxic chemotherapy also improves recurrence rates and survival, with the magnitude of benefit decreasing with increasing age. Substantial support systems are required to optimally and safely use breast-conserving approaches to local therapy or cytotoxic chemotherapy as systemic therapy. Locally advanced breast cancer (LABC) accounts for at least half of all breast cancers in countries with limited resources and has a poor prognosis. Initial treatment of LABC with anthracycline-based chemotherapy is standard and effective. Addition of a sequential, neoadjuvant taxane thereafter increases the rate of pathologic complete responses. Neoadjuvant endocrine therapy may benefit postmenopausal women with hormone receptor-positive LABC. After an initial response to neoadjuvant chemotherapy, the use of local-regional surgery is appropriate. Most women will require a radical or modified radical mastectomy. In those women in whom mastectomy is not possible after neoadjuvant chemotherapy, the use of whole-breast and regional lymph node irradiation alone is appropriate. In those women who cannot receive neoadjuvant chemotherapy because of resource constraints, mastectomy with node dissection, when feasible, may still be considered in an attempt to achieve local-regional control. After local-regional therapy, most women should receive additional systemic chemotherapy. Women with LABC that has a positive or unknown hormone receptor status benefit from endocrine therapy with tamoxifen. The treatment of LABC requires multiple disciplines and is resource intensive. Efforts to reduce the number of breast cancers diagnosed at an advanced stage thus have the potential to improve rates of survival while decreasing the use of limited resources. ■

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Breast cancer treatment guidelines have been developed for countries with a high level of resources (1–4). In this article we focus on the central aspects of treatment that should form the core of a treatment program for localized, invasive breast cancer in countries with limited resources. We define countries with limited resources collectively as those with low- or medium-level resources according to the criteria of the World Health Organization (WHO) (5).

METHODS

An international group of breast cancer experts and patient advocates met in Seattle, Washington, on October 2, 2002, to develop consensus recommendations for the treatment of breast cancer in countries with limited resources. The group, representing 17 countries and 9 world regions, followed a process initiated by the WHO to address cancer care in countries with low- or medium-level resources (5), specifically focusing on breast cancer.

In the morning, conference participants gave presentations on topics related to the treatment of breast cancer, and current approaches and barriers to treatment in countries with limited resources. In the afternoon the Treatment Panel, a subgroup of conference participants, reviewed the current evidence and existing guidelines on breast cancer treatment, debated treatment approaches under the constraints of significantly limited resources, and drafted preliminary recommendations. The final work product of this panel is the substance of this article. The methods are described fully in the overview (6).

FINDINGS AND RECOMMENDATIONS

Health Care Resources

Principles of Treatment. The treatment of invasive, local-regional breast cancer involves an assessment of the clinical and pathologic features of the breast cancer and of the health status of the woman, the application of therapy aimed at eradicating local disease in the breast and regional lymph nodes, the potential application of systemic therapy aimed at eradicating subclinical, micrometastatic disease, and follow-up after treatment for evidence of recurrent disease.

Analytic Endpoints. Assessment of the value of treatment for breast cancer may be based on a number of different endpoints or outcomes, including survival, disease-free survival, quality of life, and cost. The panel's recommendations are made considering all of these endpoints and outcomes.

Staging Systems. The use of consistent, reproducible criteria for the staging of breast cancer allows for the comparison of various treatments, the selection of appropriate treatments, and estimation of the overall prognosis. The American Joint Committee on Cancer (AJCC) and the TNM Committee of the International Union Against Cancer (UICC) have both developed TNM-based tumor staging systems that are similar and compatible (7,8). In this article we use the clinical staging system for breast cancer developed by the AJCC (7).

Early and Accurate Diagnosis Facilitates Treatment of Breast Cancer. Timely and accurate diagnosis of breast cancer is important to optimizing treatment. The treatment of early stage breast cancer is less resource intensive than that of advanced-stage breast cancer, and the outcomes are generally superior. Accurate histologic diagnosis of breast cancer is necessary to ensure that women with breast cancer are given optimal treatment and that healthy women are not erroneously given treatment for breast cancer. The availability of accurate tests for the presence or absence of estrogen (ERs) and progesterone receptors (PRs) in breast cancers is crucial for making decisions about systemic therapy. Accompanying consensus statements offer approaches for the early detection of breast cancer (9) and the diagnosis of breast cancer (10) when resources are limited.

Research. Although progress has been made in managing breast cancer, optimal treatments require further research. In countries with limited resources, large numbers of women with breast cancer are treated each year. Whenever possible, women should be encouraged to participate in simple and practical, well-designed clinical trials, as this benefits society and may benefit the woman.

STAGE I AND II DISEASE

Local Treatment

Modified Radical Mastectomy. Local treatment of stage I and II breast cancer normally requires treatment of the entire breast and the axillary lymph nodes with surgery, radiation, or a combination of both. Modified radical mastectomy is an effective local treatment for breast cancer using surgical techniques that are widely available (11). Modified radical mastectomy is a rapid treatment and is usually associated with a short posttreatment convalescence and limited long-term complications.

Modified radical mastectomy may be performed alone or in association with reconstruction. A number of breast

reconstruction techniques are available that differ greatly in the extent of surgery, complication rates, technical difficulty for the surgical team, and recovery time (12). Reconstruction of the breast provides many women with an enhanced body image and self-esteem, and better psychosocial adjustment, but it does not impact on the probability of disease recurrence or survival. Unfortunately the cost of breast reconstruction can be prohibitive in countries with limited resources, depending in part on whether that reconstruction is performed using implants, myocutaneous flap reconstruction, or a combination of the two.

Breast-Conserving Therapy. An alternative treatment to mastectomy is the use of breast-conserving surgery and radiation therapy (11,13,14). Breast-conserving therapy entails complete excision of the tumor in the breast, surgical axillary staging, and radiation therapy to the whole breast and potentially to the regional lymph node-bearing areas. Under appropriate conditions, breast-conserving therapy allows preservation of the breast and provides survival equivalent to that of a modified radical mastectomy. The main benefit of breast-conserving surgery is preservation of body image for the woman, which greatly improves her quality of life.

Breast-conserving therapy requires the following resources:

- High-quality breast imaging (mammography and ultrasound) to ensure that complete excision of the tumor is possible and is achieved.
- Surgical pathology services to ensure tumor-free margins of excision.
- Surgical services experienced in achieving a good cosmetic result while achieving a high frequency of negative pathologic margins of excision.
- Access to safe and effective radiation therapy.

Safe and effective radiation therapy, in turn, requires the following resources:

- Experienced radiation therapists.
- High-quality radiation sources.
- Radiation physics planning and high-quality treatment planning.
- Access to the therapy without long delay.
- Geographic accessibility.
- Support systems that allow a woman to receive the therapy over a period of weeks.

In special situations, wide excision of the tumor alone without radiation therapy may be considered. Studies evaluating the use of wide excision alone have found higher rates of recurrence in the local-regional area, but major differences in survival have not been observed (13,15). However, the consensus of the Treatment Panel is that women who can undergo breast preservation without radiation therapy are at best a highly selected subgroup, comprising the exception rather than the rule. Thus, although selected women may be able to forego radiation therapy with an acceptable outcome, a health care system must be able to provide radiation therapy in order to offer surgery less than modified radical mastectomy for invasive cancer.

In addition to radiation therapy, adequate breast imaging (mammography and ultrasound) is critical for assessing the extent of disease, and adequate pathology resources for evaluating surgical margins are a core resource. If it is not feasible to perform detailed margin assessment because pathology resources are unavailable, it may still be reasonable to provide local control with surgery and radiation, if it is possible to create wide (>1.0 cm) margins, after the "quadrantectomy" skin-resecting approach advocated by Italian breast surgeons such as Umberto Veronesi in the 1980s.

Postmastectomy Radiation of the Chest Wall and Regional Lymph Nodes. The chest wall and regional lymph nodes are common sites of recurrent disease after modified radical mastectomy. Risk factors for local-regional recurrences have been identified and include large tumor size, positive margins of the resection, involvement of the skin or chest wall, and a large number of involved axillary lymph nodes. In North American breast cancer treatment guidelines, postmastectomy radiation is generally recommended for tumors larger than 5 cm in maximum diameter and those with four or more involved axillary lymph nodes, those with positive surgical margins on resection, and those with involvement of the skin or underlying chest wall (1,16).

The use of postmastectomy prophylactic chest wall radiation therapy reduces the relative risk of local-regional recurrences in all groups of women, with the largest absolute risk reduction occurring in those with the highest risk for recurrent chest wall disease. Recent studies have demonstrated that radiation therapy of the chest wall and regional lymph nodes after mastectomy may also improve overall survival in women with axillary lymph node-positive breast cancer (1,16). This remains an area of substantial controversy and uncertainty (1,16). The resources needed for safe and effective postmastectomy radiation therapy are similar to those needed for breast-conserving radiation therapy (described previously).

Systemic Treatment

A substantial proportion of women with initial stage I or II breast cancer will ultimately experience relapse

of their breast cancer and death from breast cancer. A number of factors are independently prognostic for recurrence of disease, including the number of involved axillary lymph nodes, tumor size, tumor histologic grade, and tumor steroid hormone receptor content (17). These factors may be used to estimate a woman's individual risk for recurrence of disease and of death from disease when treated by local therapies alone. These same factors may also be used to predict the relative and absolute reduction in risk of recurrence and of death from breast cancer that is achieved with the use of systemic chemotherapy and/or endocrine therapy (18–20). The decision-making process regarding the use of systemic therapy is thus strongly influenced by the pathologic characteristics of the tumor, especially tumor size, number of involved axillary lymph nodes, and tumor steroid hormone receptor content.

Computer-based models for estimating the risks of breast cancer relapse and death and the benefits from adjuvant therapy in North American populations of women have been developed (21,22). The applicability of these models to non–North American populations has not been assessed.

The availability of careful pathologic assessment, including the determination of tumor ER and/or PR protein content, is central to making decisions about systemic adjuvant therapy (23,24). It is difficult to achieve accurate and reproducible results from tests for hormone receptor proteins. Fixing tumors with formalin can destroy hormone receptor proteins, particularly ER proteins. The best current technology for assessing hormone receptor proteins is immunohistochemical staining of sections of fixed and paraffin-embedded breast tumor tissues. Across different populations, approximately 55% of breast tumors will stain positive for both ER and PR proteins, 8% will stain positive for ER protein only, and 8% will stain positive for PR protein only; 29–39% of tumors will not stain positive for either receptor protein (24).

Endocrine Therapy. Many breast cancers respond to a wide variety of endocrine therapies. Benefit from these therapies may be predicted by the presence of ER and/or PR protein in the breast cancer. High-level evidence suggests that the use of adjuvant endocrine therapy in women with ER and/or PR-positive breast cancer substantially reduces the risks of disease recurrence and death (19). The benefit from endocrine therapy is substantial enough that if tests for hormone receptor proteins are not available, a breast cancer should be considered receptor positive.

The most widely used endocrine therapy is the selective estrogen receptor modulator (SERM) tamoxifen. The SERM toremifene seems to be similarly efficacious (25). Evidence suggests that 5 years of tamoxifen therapy is superior to shorter durations of therapy (19). Ten years of tamoxifen therapy provided no advantage over 5 years of therapy in two studies in women with lymph node-negative breast cancer (26,27). Ongoing studies are assessing the potential value of more than 5 years of treatment with tamoxifen.

The benefit of tamoxifen is additive to that of chemotherapy (19). Therefore the combination of tamoxifen and cytotoxic chemotherapy provides benefits greater than the benefits from either therapy alone. Tamoxifen is associated with toxicity, including hot flashes and a low risk of thromboembolic disease, endometrial carcinoma, and cataracts. In postmenopausal women, tamoxifen appears to maintain bone mineral density. In women with hormone receptor-positive tumors, tamoxifen reduces the risk of second, contralateral breast cancers.

Recent evidence from a trial with relatively short follow-up suggests that the selective aromatase inhibitor anastrozole is superior to tamoxifen for achieving disease-free survival in the adjuvant treatment of receptor-positive invasive breast cancer in postmenopausal women (28). The absolute difference between anastrozole and tamoxifen in terms of disease-free survival is small and must be balanced with the substantially higher cost of selective aromatase inhibitors. This trial and the results of other trials of selective aromatase inhibitors should provide more information to better assess the impact of these agents in this setting. At present, tamoxifen or anastrozole is appropriately used as adjuvant endocrine therapy in postmenopausal women. The aromatase inhibitors should *not* be used in the treatment of invasive breast cancer in premenopausal women.

Ovarian ablation (e.g., surgical oophorectomy or radiation ablation) or suppression (e.g., use of the gonadotropin-releasing hormone or luteinizing hormone-releasing hormone analogues) with or without tamoxifen is an effective therapy in the treatment of breast cancer in premenopausal women (20,29,30). Early studies of ovarian ablation or suppression in premenopausal women unselected for the hormone receptor status of their breast cancer found disease-free and overall survival equivalent to that of CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) chemotherapy (20,31). Recent studies demonstrate that ovarian ablation plus tamoxifen may be superior to CMF chemotherapy in premenopausal women with hormone receptor-positive breast cancer (30). Indirect evidence also suggests that the addition of tamoxifen to ovarian ablation may provide additional

benefit. In premenopausal women with hormone receptor-positive breast cancer, oophorectomy plus tamoxifen may be considered an appropriate adjuvant endocrine therapy and is likely to be a cost-effective strategy compared with chemotherapy alone.

Cytotoxic Chemotherapy. Cytotoxic chemotherapy has an established role in the treatment of women with invasive breast cancer (18). In general, combination chemotherapy is superior to single-agent chemotherapy. In addition, the magnitude of risk reduction for recurrence or death achieved with combination chemotherapy decreases with increasing age. The efficacy of cytotoxic chemotherapy in women older than 70 years remains uncertain. The benefits achieved with cytotoxic chemotherapy are additive to those achieved with tamoxifen (19).

A number of effective cytotoxic chemotherapy regimens exist and the antitumor efficacies of these regimens are similar. In unselected women, anthracycline-containing chemotherapy appears to be superior overall to CMF chemotherapy (18). The addition of sequential taxane chemotherapy to anthracycline-based chemotherapy may be superior to anthracycline-based chemotherapy alone (32). Classical (oral) CMF proved to be equivalent to anthracycline-based chemotherapy in several clinical trials and represents an effective and less expensive adjuvant chemotherapy regimen (33).

Cytotoxic chemotherapy often requires intravenous administration and may be associated with serious and sometimes life-threatening complications. The use of cytotoxic chemotherapy thus requires the following resources:

- Laboratory facilities to monitor white blood cell, red blood cell, and platelet counts.
- The ability to monitor cardiac function (echocardiography, electrocardiography).
- Pharmacy services to compound the drugs.
- Antiemetics.
- Infusion facilities to administer intravenous chemotherapy.
- Medical services to monitor and manage the toxicities of treatment (microbiology and general laboratory facilities, transfusion services for red blood cells and platelets, growth factors, hydration facilities, broad-spectrum antibiotics, and pulmonary and cardiac support systems).

Surveillance After Treatment. After the treatment of breast cancer, women are at risk for the development of recurrent disease. Follow-up of women for recurrence of breast cancer after treatment includes history and physical examinations at increasing time intervals in conjunction with yearly mammograms, and in women taking tamoxifen, pelvic examination. The use of surveillance chest radiographs, echocardiograms, computed tomography, and blood chemistries has not been found to substantially aid the diagnosis of recurrent disease or to enhance overall survival (34–36).

Stage III and Localized Stage IV Disease

Locally advanced breast cancer (LABC) encompasses breast cancer with a wide range of biologic behaviors. It includes large breast cancers (T3 tumors, those larger than 5 cm in diameter), those with advanced involvement of regional lymph nodes (N2, ipsilateral axillary lymph nodes fixed to surrounding structures or to each other; N3, ipsilateral internal mammary lymph node involvement), T4 tumors (chest wall involvement, edema, or ulceration of the skin; presence of satellite nodules; inflammatory carcinoma), and those with ipsilateral supraclavicular lymph node involvement as the only evidence of distant metastasis.

LABC represents 50–80% of all breast cancer cases in countries with limited resources (37,38). Approximately half of the women die of their disease within 5 years of diagnosis. The treatment of LABC is multidisciplinary, requires extensive staging, and normally requires the use of chemotherapy, surgery, and radiation therapy. LABC is thus an important health problem that consumes substantial resources in these countries. Such resources could be used more effectively if these cancers were detected at an earlier stage.

Compared with the treatment of LABC, the treatment of early stage breast cancer expands the available treatment options, improves overall disease outcome, and uses fewer resources. Thus efforts to diagnosis breast cancer earlier have both medical and fiscal advantages.

Neoadjuvant Chemotherapy

Initial treatment of LABC with anthracycline-based chemotherapy for four to six cycles is a standard and effective treatment (39). The addition of a sequential, neoadjuvant taxane after anthracycline-based neoadjuvant chemotherapy has been demonstrated to increase the rate of pathologic complete responses compared with anthracycline-based chemotherapy alone (40). Recent evidence suggests that neoadjuvant endocrine therapy may be beneficial in postmenopausal women with hormone receptor-positive disease (41).

Local-Regional Control for LABC

After an initial response to neoadjuvant chemotherapy, the use of local-regional surgery is appropriate. Most

women will require a radical or modified radical mastectomy. Selected women may be treated with wide local excision and whole-breast and regional lymph node irradiation. In those women in whom mastectomy is not possible after neoadjuvant chemotherapy, the use of whole-breast and regional lymph node irradiation alone is appropriate. In those women with LABC who do not have access to neoadjuvant chemotherapy because of economic constraints, mastectomy with node dissection, when feasible, may still be considered in an attempt to achieve local-regional control.

The principles for safe and effective radiation therapy are the same as those for stage I and II breast cancer (described previously). Resource constraints are at least as limiting as those for early stage disease. Because radiation therapy protocols are typically more complex and technically demanding for LABC than those for early stage disease, proper treatment of LABC with radiation therapy is typically even more difficult under conditions of limited health care resources.

Chemotherapy After Local-Regional Therapy for LABC

After local-regional therapy, most women should be treated with additional systemic chemotherapy. A number of chemotherapy regimens may be considered in this situation; generally, a chemotherapy regimen not used for neoadjuvant chemotherapy is preferred.

The principles for safe and effective systemic chemotherapy are the same as those for stage I and II breast cancer (described previously). Resource constraints are at least as limiting as those for early stage disease. Because chemotherapy protocols for LABC are typically more complex and toxic than those for early stage disease, proper treatment of LABC with systemic therapy is typically even more difficult under conditions of limited health care resources.

Endocrine Therapy for LABC

Women with LABC that is positive for ERs and/or PRs or that has an unknown receptor status benefit from "adjuvant" (or maintenance) endocrine therapy with tamoxifen.

CONCLUSION

The optimal treatment of breast cancer requires the ability to diagnose the disease early and accurately. Local treatment of early stage breast cancer involves either breast-conserving surgery followed by whole-breast irradiation. The pathologic and biologic properties of a woman's breast cancer may be used to estimate the probability for recurrence of and death from breast cancer, and to estimate the relative and absolute magnitude of benefit the woman is likely to receive from adjuvant endocrine therapy or cytotoxic chemotherapy. Substantial support systems are required to optimally and safely use breast-conserving approaches or cytotoxic chemotherapy as systemic therapy.

LABC is a common form of breast cancer in countries with limited resources and is associated with a poor prognosis. The treatment of LABC requires the availability of multiple disciplines and is relatively resource intensive. Efforts to reduce the number of breast cancers diagnosed at an advanced stage thus have the potential to improve rates of survival while decreasing the use of limited resources.

PANELISTS

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