



**BREAST
CANCER
INITIATIVE^{2.5}**
Making breast health a global priority

TREATMENT

Systemic Therapy: Chemotherapy for Breast Cancer

Knowledge Summary

Systemic Therapy: Chemotherapy for Breast Cancer

INTRODUCTION

Chemotherapy plays a central role in the treatment of breast cancer for the majority of patients at all resource levels. Chemotherapy improves survival, reduces recurrence and has the capacity to improve candidacy for definitive surgery or for breast conservation when used before surgery. It can also be used to palliate painful symptoms of advanced disease. Over the past 35 years, the effectiveness of systemic therapy (including chemotherapy) has improved and together with increased efforts in early detection, systemic therapy has contributed to major improvements in breast cancer survival. Studies suggest that tumor biology (which may differ among patients) affects response to chemotherapy, thus requiring tumor pathology studies prior to initiation of treatment regimens. The toxic side-effects of chemotherapy and the resources to monitor for and manage toxicity must be considered in chemotherapy treatment planning.

Depending on the stage at diagnosis and the specific biologic features of a given breast cancer, systemic therapy for breast cancer can include chemotherapy, hormonal therapy and targeted agents (see Systemic Therapy: Hormonal Therapy and Targeted Agents). Systemic therapy can be administered preoperatively (neoadjuvant therapy), postoperatively (adjuvant therapy), or for metastatic disease. Determining the appropriate systemic therapy requires pathologic confirmation of breast cancer, the tumor stage, and, if available, the hormone receptor and HER2 status of the tumor (see Diagnosis: Biopsy, Pathology and Subtypes). The recommendations for chemotherapy vary by patient, tumor, cost and resource availability (see Table 2).

Even when chemotherapy is available, many women with breast cancer in low- and middle-income countries (LMICs) cannot afford the recommended treatments and those who are able to afford chemotherapy often discontinue therapy before treatment is completed. Because most studies involving chemotherapy occur in high-resource settings, it is a challenge to translate these findings into effective strategies for chemotherapy regimens in low-resource settings. Studies are needed in LMICs to establish evidence-based treatment best practices within these settings.

KEY SUMMARY

Chemotherapy

- The principle of cytotoxic chemotherapy is to kill cancer cells without excessive injury to the body's normal cells.
- There are many different types of chemotherapy medications. The most common agents used in breast cancer care are alkylating agents, antimetabolites, anthracyclines and mitotic inhibitors.
- The recommendations for chemotherapy vary by patient, tumor, cost and resource availability and require an accurate diagnosis.
- The toxic side-effects of chemotherapy and the resources to monitor for and manage toxicity must be considered in chemotherapy treatment planning.

Provision of essential chemotherapy medicines

- Support availability and access to chemotherapy agents and all medicines required to treat chemotherapy-induced side effects at the basic level. Five chemotherapy medications commonly used to treat breast cancer are included in the 2015 WHO Model List of Essential Medicines (see www.who.int/medicines/publications/essentialmedicines/en/).
- Ensure key chemotherapy agents are available, safely stored and administered appropriately in accordance with local regulations.
- Reduce cost of essential chemotherapy medicines to patient (patient out-of-pocket costs) to improve access to essential medicines.

Protocols for preoperative and postoperative chemotherapy

- Improve access to postoperative (adjuvant) chemotherapy to decrease the probability of cancer recurrence and reduce the likelihood of death from breast cancer.
- For women with large tumors, consider neoadjuvant (preoperative) chemotherapy to reduce tumor size and improve the likelihood of successful surgery.
- Confirm that selected combination therapy protocols follow evidence-based guidelines for breast cancer treatment.
- Consider additional studies to further define chemotherapy regimens in limited resource settings.

Health systems and workforce capacity

- Safe and effective chemotherapy administration is best delivered by specially trained personnel including medical oncologists and oncology nurses. When oncology specialists are not available, provide specialized oncology training and develop environment-specific standardized oncology protocols, procedures and processes to be managed by non-oncology staff.
- Establish that necessary support services, such as laboratory and patient services to monitor and manage treatment related toxicities, are available and accessible to all patients at all times and that these support services are required during the treatment protocol.
- Ensure that multidisciplinary teams and patient navigators are available for encouraging patient adherence to the treatment plan throughout its course.

Resource-stratified pathways across the continuum of care

- Develop programs based on identified needs and barriers, outcome goals and available resources.
- Pursue a defined resource-stratified pathway to ensure coordinated investment and incremental program development across the continuum of care.



POINTS FOR POLICYMAKERS:

OVERVIEW

Preplanning

- Identify data sources to estimate disease burden.
- Identify who will lead the process, and identify what stakeholders to engage.

Planning Step 1: Where are we now?

Investigate and assess

- Examine data and estimate the potential need for systemic therapy.
- Assess health system capacity including pathology services, treatment protocols, safety standards and supportive services.
- Identify structural, sociocultural, personal and financial barriers to delivery of systemic therapy.

Planning Step 2: Where do we want to be?

Set objectives and priorities

- Consider how to make appropriate chemotherapy regimens available to all breast cancer patients.
- Identify gaps in training, expertise and health care capacity.
- Consider implementation of policies that ensure availability of the essential chemotherapy drugs as recommended by WHO.
- Assess feasibility of interventions and how to balance clinical benefit to the patient, cost to the health care system and equitable access to systemic therapies.

Planning Step 3: How do we get there?

Implement and evaluate

- Follow a resource-stratified pathway for delivery of chemotherapy.
- Develop standard protocols for delivering chemotherapy that consider tumor characteristics, stage and prognosis and preferences of the patients.
- Invest in oncology training and recruitment and retention of medical oncologists and oncology nurses.
- Strengthen capacity to safely and effectively administer available systemic therapy.

WHAT WE KNOW

Chemotherapy: The principle of cytotoxic chemotherapy is to kill cancer cells without excessive injury to the body's normal cells. Chemotherapy can lead to selection of chemoresistant tumor cells after which a given chemotherapy agent will no longer have an antitumor effect. Changing the chemotherapy (i.e., sequential therapy strategy) and/or using an agent of a different class (i.e., non-cross-resistant strategy) may improve tumor response. Most adjuvant chemotherapy regimens use more than one agent, as polychemotherapy has been shown to result in better survival of patients with nonmetastatic breast cancer than single agent chemotherapy. However, combinations may have more toxicity and require more sophisticated support systems to help patients complete treatment. Evidence-based guidelines on chemotherapy for breast cancer should be followed and efforts should be made to ensure patients complete the prescribed course of treatment.

Types of agents: There are many different types of chemotherapy medications. The most common agents used in breast cancer care are alkylating agents, antimetabolites, anthracyclines and mitotic inhibitors:

- Alkylating agents cause direct damage to DNA, prevent cancer cells from reproducing and work in all cell cycle phases. Alkylating agents can be subdivided into classes, such as the nitrogen mustards (e.g., cyclophosphamide). Platinum agents are alkyl-like anti-neoplastic agents.
- Antimetabolites include 5-fluorouracil (5-FU), gemcitabine and methotrexate. Antimetabolites cause damage during the S-phase of the cell cycle, when DNA is replicated, thereby preventing cell division and tumor growth.
- Anthracyclines (e.g., doxorubicin, epirubicin) are antitumor antibiotics that affect all phases of the cell cycle and cause cell damage and death.
- Mitotic inhibitors include taxanes (e.g., paclitaxel, docetaxel) and vinca alkaloids (e.g., vincristine). Mitotic inhibitors work during the M, or nuclear division, phase of the cell cycle but can damage cells in any phase.

Timing: Chemotherapy regimens vary from traditional three-week schedules to a two-week (i.e., dose-dense therapy), or even a weekly schedule that may be appropriate for some women with early-stage breast cancer. The balance of effective dose versus toxic side effects requires careful management and should be administered by medical oncologists or specially trained personnel. A delay in receiving chemotherapy in early stage breast cancer has been associated with worse outcomes. Postoperative chemotherapy should not be delayed longer than 12 weeks.

Locally advanced breast cancer: In low-resource settings, 50–80% of women diagnosed with breast cancer present with advanced or locally advanced disease. LABC includes all stage III tumors, those that involve the skin or the underlying muscles of the chest and patients with fixed axillary (armpit) lymph nodes or extensive lymph node involvement. Inflammatory breast cancers (IBCs) are an especially aggressive presenta-

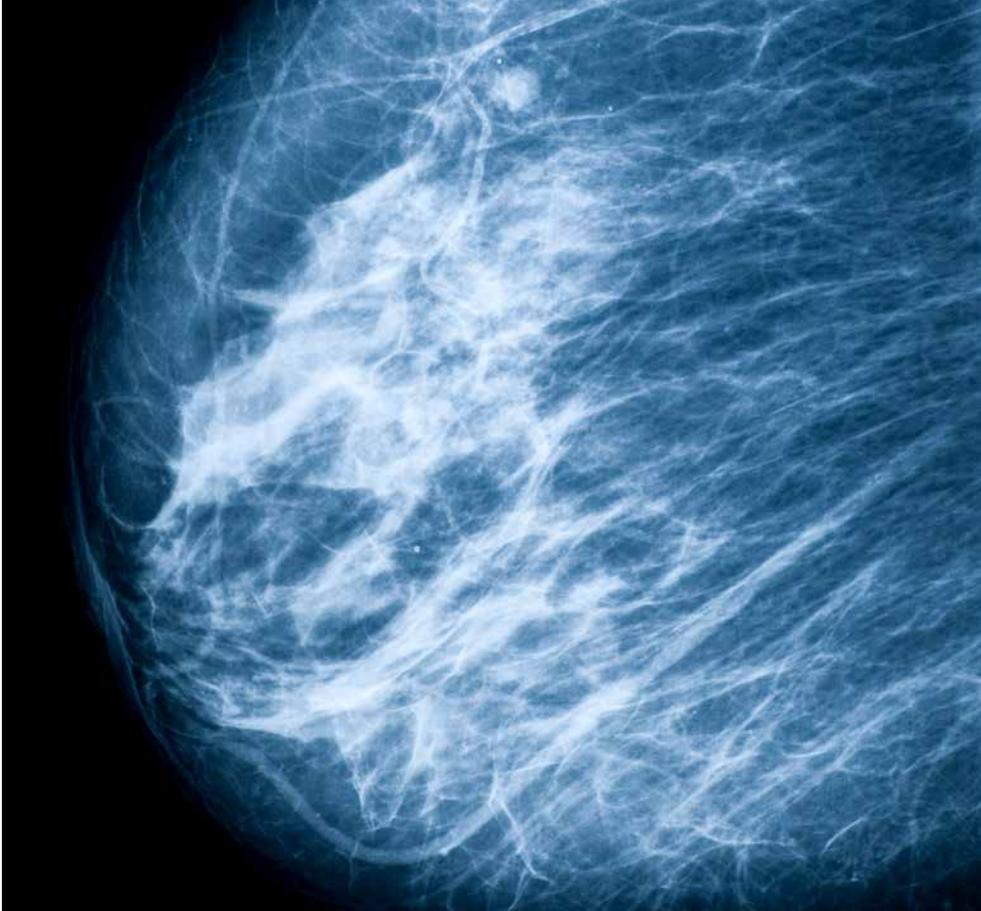
tion of LABC, where the breast appears inflamed but actually has tumor cells blocking the lymphatic vessels, resulting in swelling and redness. Any woman with clinical breast exam findings suggesting IBC (e.g., thickening and swelling of the breast, warm to touch, painful, often without a discrete mass) should be promptly referred for evaluation by a surgeon familiar with breast oncology. IBC is often initially diagnosed as a breast infection (mastitis). When these patients fail to respond to antibiotics for two to three weeks, they should undergo a diagnostic workup for cancer. Significant delays in establishing a diagnosis of IBC can worsen outcomes (see Table 1).

Neoadjuvant chemotherapy: Neoadjuvant (preoperative) therapy for LABC can reduce inoperable tumors to a resectable state. For larger tumors, it may increase the likelihood of successful breast conserving therapy (BCT). Studies suggest disease-free survival is equivalent between neoadjuvant and adjuvant (postoperative) chemotherapy, making both approaches reasonable in women with operable breast cancer. In LMICs, where most women present with LABC, more than half of advanced tumors can potentially be down-staged with chemotherapy, improving surgical options. Women with early stage breast cancer (stage I or II) are also candidates for neoadjuvant therapy if BCT is not initially possible (e.g., due to high tumor-to-breast ratio without achievable favorable cosmetic option) or if the tumor biology is aggressive.

Neoadjuvant chemotherapy therapy options depend on the tumor subtype (see *Diagnosis: Biopsy, Pathology and Subtypes*), the patient's age and comorbidities and available resources. Generally, women with breast cancer who meet the criteria for neoadjuvant therapy can be treated with appropriately selected multi-agent chemotherapy regimens. The National Comprehensive Cancer Network (NCCN) provides guidelines for chemotherapy administration.

Additional preoperative systemic therapies, such as primary endocrine or HER2-based therapy, may be considered based on tumor characteristics. HER2-positive cancers respond favorably to chemotherapy when given in conjunction with HER2-directed therapies, such as trastuzumab. The use of endocrine therapy in the preoperative setting has not been widely utilized and is generally limited to postmenopausal women who cannot tolerate or refuse chemotherapy. In low-resource settings, endocrine therapy is more accessible and may be considered for preoperative therapy if chemotherapy is not available. The duration of neoadjuvant endocrine therapy may need to be extended compared to chemotherapy and endocrine therapy should also be given after surgery (see *Systemic Therapy: Hormonal Therapy and Targeted Agents*).

Adjuvant therapy: Adjuvant (postoperative) therapy occurs after primary surgical therapy. Not every woman with breast cancer will benefit from adjuvant therapy. The goal of adjuvant chemotherapy and/or hormonal or targeted therapy delivered after surgery is to reduce breast cancer recurrence. In early stage breast cancer (i.e., stage I or II), risk factors and genetic markers can predict which patients are most likely to benefit from treatment. Predictive factors include the number of



involved axillary lymph nodes, tumor size and histologic grade and hormone receptor status. These variables also affect the likelihood of recurrence and death from breast cancer. Adjuvant therapy should be directed toward high-risk women.

Lymph node involvement: Because preoperative therapy can affect pathologic findings (e.g., tumor size, lymph node involvement), radiopaque clips are often placed in the tumor to aid in subsequent locoregional treatment (surgery and radiotherapy) before preoperative therapy, especially if breast conservation is anticipated. This helps the surgeon localize the site of the original tumor and remove it if it has responded completely to preoperative therapy. Although there is no consensus on the management of the axillary nodal beds, in HIC-suspicious lymph nodes (identified on physical exam or ultrasound) often undergo fine needle aspiration (FNA) or core needle biopsy to confirm cancer spread before preoperative therapy is administered. If a positive lymph node is confirmed, subsequent regional management will be needed, but will vary based on disease stage, resources, expertise and patient preference. In general, patients with multiple lymph node-positive breast cancer should receive chemotherapy either before or after surgery.

Lymph node-negative breast cancer: Patients with node-negative breast cancer are at risk for recurrence, particularly those with cancers that have aggressive biologic features based on tumor marker assessment. These patients may benefit from adjuvant chemotherapy. In general, women with lymph node-negative, estrogen receptor (ER)-negative breast cancer and a tumor size > 0.5 cm and/or HER2-positive tumors and ER-positive breast cancer with high-risk features should be considered for adjuvant chemotherapy. A variety of chemo-

therapy regimens can be used, including four cycles of doxorubicin and cyclophosphamide (AC) or six cycles of CMF. Some adjuvant therapy regimens also include a taxane (paclitaxel or docetaxel). [see www.nccn.org]

Metastatic disease: Metastatic breast cancer has a median survival of two years, although some patients may live many years with metastatic breast cancer. The goal of chemotherapy for metastatic breast cancer is to reduce disease-related symptoms without causing excessive treatment-related toxicities; systemic treatment can only modestly extend survival. Patients with symptomatic metastatic disease or hormone receptor-negative breast cancer should be considered for chemotherapy, whereas patients with hormone-sensitive indolent disease should be considered for endocrine therapy (see *Systemic Therapy: Hormonal Therapy and Targeted Agents*).

Combination chemotherapy has higher rates of response and longer time to first disease progression compared with single agent therapy; although it has not been shown to prove improve overall survival. Combination chemotherapy has higher rates of treatment-related toxicities and therefore sequential single agent chemotherapy is preferred for metastatic breast cancer unless a rapid response is required for symptom control.

The simultaneous use of endocrine therapy with chemotherapy has not demonstrated any survival advantage. Medication selection should be based on the goals of treatment (symptom control), prior systemic therapies, tumor subtype, resource availability, toxicity and cost. Possible cytotoxic agents include anthracyclines, taxanes, capecitabine, vinorelbine, cyclophosphamide, methotrexate, gemcitabine, ixabepilone, platinum agents and eribulin.

Common chemotherapy toxicities include nausea, vomiting, bone marrow suppression, mucositis, neuropathy, fatigue and vasomotor symptoms. Close surveillance and evaluation for these treatment-related adverse effects must be part of the routine health system administration of chemotherapy [see *Supportive Care during Treatment for Breast Cancer*].

Pregnancy-associated breast cancer: Pregnancy-associated breast cancer is defined as breast cancer diagnosed during pregnancy, in the first postpartum year or during lactation. Pregnancy-associated breast cancers tend to present at a later stage. Any breast mass in a pregnant woman should be evaluated. If mammography is used a lead shield should be put in place to protect the fetus. Ultrasonography can be a valuable adjunct. A biopsy should be performed on any suspicious finding.

Breast and axillary surgery during any trimester of pregnancy appears to be associated with minimal fetal risk, although there may be a slightly increased risk of infant mortality and low birth weight. BCT can only be offered if radiation can be postponed until after delivery as pregnant women cannot receive radiation therapy due to the risk to the fetus. Anthracyclines and cyclophosphamide do not cross the placental barrier and are safe to administer to the mother in the second and third trimesters. Tamoxifen should be avoided in pregnancy as it may cause birth defects. Breastfeeding should be avoided while receiving chemotherapy, targeted agents or hormonal therapy, as these agents may enter the breast milk. Informed consent is a critical component of choosing a treatment regimen. Preferably, women with pregnancy-associated breast cancer should be managed by a multidisciplinary team with expertise in maternal child health and breast cancer.

Treatment monitoring: Women receiving neoadjuvant systemic therapy should be monitored for disease progression. Assessment is usually done by physical exam with or without ultrasound. Generally treatment should be modified if there is evidence of tumor progression. If there is no evidence of tumor progression, treatment can proceed until completion of the planned chemotherapy cycles (usually up to eight cycles). At the completion of therapy, patients who do not have inflammatory breast cancer may be considered for BCT, depending on disease presentation. If BCT is performed, it should be followed by radiotherapy to reduce recurrence risk in the breast and/or lymph node bed. Surgery should still be performed even when the tumor appears to have completely resolved based on breast examination and imaging. Patients with inflammatory breast cancer have a high rate of local recurrence and should be treated with mastectomy and radiotherapy even when a complete response to preoperative therapy is observed.

Safety considerations: Cytotoxic chemotherapy usually requires intravenous administration by an experienced health professional who is aware of and able to manage short- and long-term toxicities. Chemotherapy can be associated with serious and potentially life-threatening toxicities [see *Supportive Care During Treatment for Breast Cancer*]. To safely administer chemotherapy, the following resources should be available: laboratory facilities [e.g., for complete blood count], pharmacy services for dispensing drugs, infusion facilities for administering drugs and service to manage toxicities [e.g., blood transfusions, microbiology laboratory]. Pathology services that measure hormone receptor status and tumor markers are required to identify candidates for hormone or targeted therapies. Many of the newer systemic treatments require more complex pathology services that may not be appropriate or available in low- or even middle-resource settings.



WHAT WORKS

Partnerships and collaborations: Multisectoral collaboration involving medical and patient associations, industry and other stakeholders can be engaged to help improve the availability of appropriate treatment options. Decisions should be based on the available efficacy data, costs, health system capacity and community support. Multisectoral collaborations can also promote continuing medical education and the development of infrastructure for clinical trials with appropriate regulatory monitoring, ethical guidelines and oversight.

Health professional training: Due to shortages of medical oncologists in low-resource settings, systemic therapy is often administered by radiation therapists, surgeons and primary care physicians. Training of medical oncologists should be a priority and nonmedical oncologists who administer chemotherapy should be provided continuing medical education and evidence-based cost-effective chemotherapy guidelines. As medical oncologists become trained in a region and advanced therapies become available, multimodal therapy can be considered. Multidisciplinary teams and tumor boards can strengthen systemic therapy programs. Treatment recommendations must consider tumor biology, local community resources, patient and health professional safety issues and available supportive care for toxic side effects of chemotherapy.

Coordination of services: A multidisciplinary approach supports the use of treatment guidelines across care settings and sharing of critical patient information to improve care, minimize delays in therapy, reduce duplication of services and optimize outcomes. Multidisciplinary teams can include a full range of experts [surgeons, primary care clinicians and nurses, radiologists, medical oncologists, pathologists] or, in LMICs only two or three specially trained team members (e.g., surgeon, nurse, radiologist). This is particularly important with LABC as response to preoperative therapy affects subsequent treatment decisions. Tumor boards provide an opportunity for multidisciplinary teams to participate in formal cancer treatment planning for each patient. In some settings, when medical oncologists are not available, non-oncologist physicians can be responsible for chemotherapy preparation and administration.

Successful delivery of chemotherapy to patients requires efficient administration of the chemotherapy supply chain, which includes monitoring, handling (short- and long-term storage) and equitable distribution. International agencies regulate licensing, production of generic medicines and counterfeit medicines; however, procedures to identify and remove counterfeit and substandard medicines should be in place. Regional

and local health authorities should set standards for the level of expertise required to prescribe and administer chemotherapy. Health systems that follow WHO goals will ensure that essential medicines are prescribed safely, tested for quality [i.e., stability and ingredient quality]; and require suppliers to provide documentation of compliance with regulatory specifications.

Standardized protocols: Where there are shortages of medical oncologists, explicit chemotherapy protocols with clear start-stop rules can be used to standardize chemotherapy and should include procedures and resources to manage toxic side effects including dose reductions. Protocols should be updated as new therapies and expertise become available. Proper dosing is important and must be individualized to a patient's body-mass index, balancing priorities of optimal effects and minimal toxicities. Comorbidities, such as malnutrition, tuberculosis, malaria or hepatitis may have a major effect on chemotherapy tolerance and should be managed as part of a treatment plan. Resource-appropriate treatment guidelines can help ensure appropriate chemotherapy choices [see Table 2].

Cost-effectiveness and financing: The cost-effectiveness of chemotherapy will vary by region and on the basis of epidemiologic and economic factors. Calculating the cost-effectiveness of chemotherapy is complex; many factors affect cost-effectiveness, including the relative benefits of a new therapy compared to its cost [including costs related to managing treatment related side effects, and its efficacy when compared to standard treatments. Additional studies are needed to identify the most cost-effective regimens, including duration of treatment at different resource levels. National cancer budgets should include the purchase of essential medications and consider subsidizing patient costs. In low-resource settings, patients are often required to pay out-of-pocket for a significant portion of medications, which can result in a failure to initiate or complete treatment out of concern for their family's financial well-being.

Access to treatment: Lack of patient adherence to treatment in low-resource settings may be attributed to structural, sociocultural, personal and financial barriers to care (e.g., location, transportation, finances) or complexity and timing of care [chemotherapy regimen that can range from once every three weeks for six months or longer]. Government subsidization of public hospital fees and/or transportation may improve patient adherence. Providing community support and patient navigation may also improve adherence to treatment. Health education, advocacy, patient support groups, home visits and monitoring and tracking of breast cancer patients can help reduce nonadherence and loss to follow up.

PLANNING STEP 1: WHERE ARE WE NOW?

Investigate and assess

Assess the need for chemotherapy

- Examine data on breast cancer stage at diagnosis, tumor size, subtype and lymph node involvement to inform health system needs and drug planning.

Assess existing services and protocols

- Review national or regional guidelines for the use of chemotherapy and tailor them to local resources and tumor biology.
- Chemotherapy protocols should include types of chemotherapeutic agents used, indications for use, dosing schedules, type and training of personnel, availability of core services (e.g., pathology laboratories) and safety and quality metrics.

Assess patient access and barriers to providing chemotherapy

- Identify structural, sociocultural, personal and financial barriers to access and delivery of chemotherapy.
- Consider health system barriers including cost of medicines, lack of a reliable supply chain and shortages of trained health professionals who can prescribe and administer chemotherapy safely and monitor patients for short- and long-term treatment-related toxicities.
- Consider patient barriers to chemotherapy including cost, logistics and side effects that reduce adherence to treatment regimens.

Assess health system capacity

- Assess the number and types of chemotherapeutic agents procured by the ministry of health, regulatory process and supply chain, price factors (to the government and to the patient), consumption per health care facility and reported shortages and safety concerns.
- Assess the regulatory and administrative process responsible for the review, approval and implementation strategy for new treatments.
- Review diagnostic capacity, training and education, safety and quality assurance measures and supportive services.

Assess monitoring and evaluation capacity

- Review health system monitoring of time from diagnosis to treatment as a quality metric.
- Assess tracking of consumption of systemic therapies and provider use of treatment protocols.
- Evaluate protocols, accessibility, quality of care and adherence to treatment regimens to ensure high-quality and effective treatment.

PLANNING STEP 2: WHERE DO WE WANT TO BE?

Set objectives and priorities

Define target population and approach

- Use available data on cancer incidence and demographic data to estimate the population that could benefit from systemic therapy.

Identify gaps

- Ensure pathology expertise and capacity is in place, supported by standard diagnostic protocols.
- Identify gaps in training and expertise of health professionals in the administration and management of systemic therapies.
- Identify any regulatory and/or ethical approval processes needed for the introduction of systemic therapy.

Set achievable objectives

- Consider specific program improvements such as increasing volumes of chemotherapy available, expansion of oncology-trained staff and coordination of chemotherapy-related services.
- Investigate establishing a regulatory process to effectively purchase and deliver chemotherapy medications, starting with the five essential medicines.
- Establish multisectoral partnerships to advocate for reduced cost chemotherapy medicines.
- Consider a proactive training, recruitment and retention plan for medical oncology specialists.
- Develop well-defined quality assurance measures that address safe administration and handling of chemotherapy.

Set priorities and determine feasibility of interventions

- Follow a resource-stratified pathway for program development that identifies available resources across the continuum of care.
- Consider options to minimize the financial impact of patient out-of-pocket expenses.

PLANNING STEP 3: HOW DO WE GET THERE?

Implement and evaluate

Establish partnerships and financing

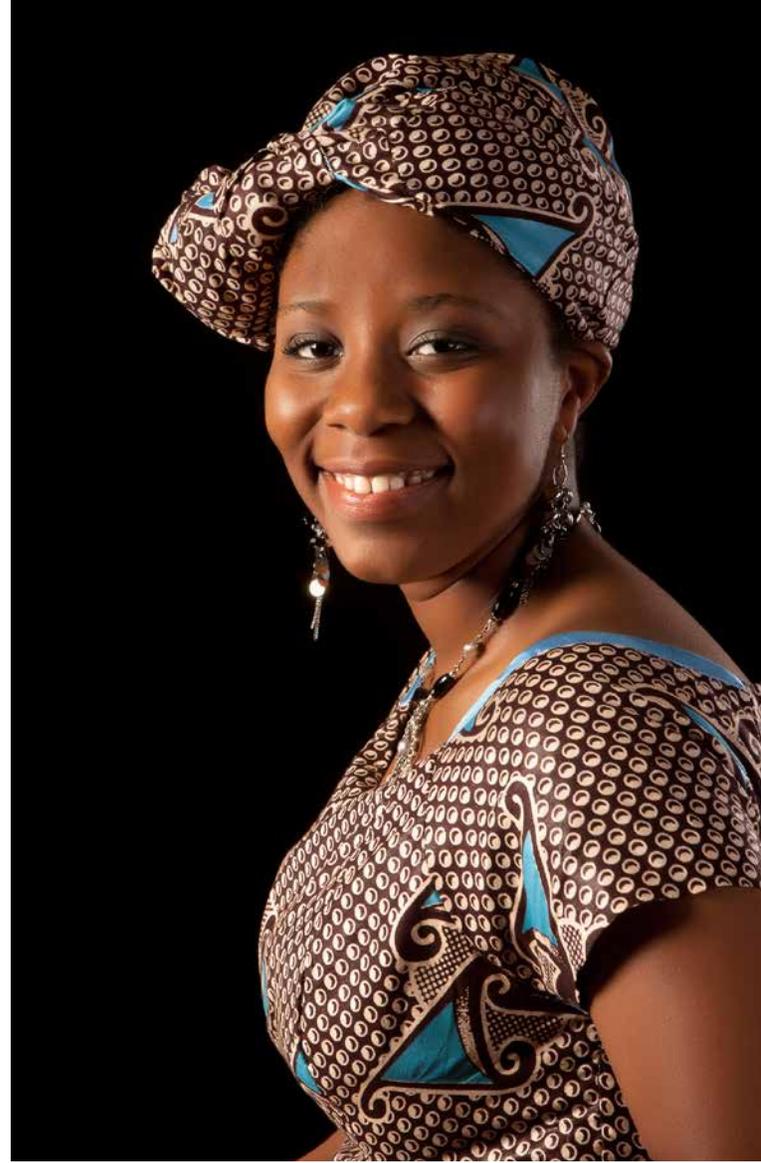
- Secure necessary political and financial support for program interventions.
- Strategies to reduce costs should include multisectoral collaborations and prioritize the WHO Model List of Essential Medicines.

Launch, disseminate and implement

- Address gaps in the availability and safe delivery of chemotherapy.
- Invest in oncology training and recruitment and retention of medical oncologists and oncology nurses.
- Secure access to care for all populations.
- Collaborate with academic societies, government and key stakeholders to develop and implement standardized guidelines and standards of care.
- Counsel health care providers on treatment protocols to ensure patients receive safe and effective therapy.
- Breast cancer diagnosis and treatment is complex and coordination of care between facilities can improve patient satisfaction and adherence to treatment plans. Core services include surgery, pathology, pharmacy, primary care routine evaluation and care of treatment-related toxicities.
- Develop research priorities as a component of treatment services to establish updated standards of testing, duration of therapy, surveillance of toxicities and determination of the economic burden of treatment and other barriers.
- Balance the development of specialized services at cancer centers with the strengthening of referral networks and reducing financial and structural health system and patient barriers to care.

Monitor and evaluate

- Establish assessment, process and quality metrics and outcomes measures.
- Review biopsy procedures and pathology quality assurance programs to ensure accurate diagnosis.
- Conduct surveillance of health professional adherence to treatment protocols and guidelines for systemic therapy.
- Anticipate, monitor and manage treatment-related toxicities.
- Document the administration and outcomes of systemic therapy in health records, preferably in a centralized system. This will allow for safety monitoring, quality assurance, surveillance of counterfeit and substandard medicines, tracking of outcomes and establishing standards of care.



CONCLUSION

Chemotherapy is a core component of breast cancer treatment. In LMICs, where locally advanced and hormone-receptor negative breast cancer is common at presentation, the benefit of chemotherapy can be significant. The use of chemotherapy can contribute to a reduction in deaths among women with breast cancer. Studies have shown chemotherapy has the potential to improve surgical candidacy at all resource levels. However, there are many unanswered questions regarding the best delivery, dosing, administration, cost and effectiveness of chemotherapy, particularly in LMICs. Approaching chemotherapy as a multidisciplinary team effort, adopting a multisectoral approach to the acquisition of chemotherapy agents and supportive care services, health professional training in safe and timely administration of chemotherapy, development of resource-stratified guidelines and support for research in chemotherapy in LMICs is needed.

Table 1. Locally advanced breast cancer (LABC): operable and inoperable categories

Operable or Inoperable	Stage category
LABC that may be operable at presentation	Stage IIIA: T3 with N; N2 with any T1-T3
LABC that is inoperable at presentation	Stage IIIB: T4, skin;T4b, chest wall; T4c (a+b)
Inflammatory breast cancer	T4d

Abbreviations: **LABC**, locally advanced breast cancer; **T**, tumor, **N**, lymph node

Source: El Saghir NS, Eniu A, Carlson RW, Aziz Z, Vorobiof D, Hortobagyi GN. Breast Health Global Initiative Systemic Therapy Focus Group. Locally advanced breast cancer: treatment guideline implementation with particular attention to low- and middle-income countries. *Cancer*. 2008 Oct 15;113(8 Suppl):2315-24.

NOTE: * The following drugs are used in the most common breast cancer chemotherapy regimens.

Cyclophosphamide, doxorubicin (or epirubicin), 5-fluorouracil, methotrexate, paclitaxel (or docetaxel).

Table 2. Systemic therapy recommendations by disease stage and resource level

Disease stage	Resource level	Neoadjuvant chemotherapy [preoperative]	Adjuvant chemotherapy and/or hormonal or targeted therapy [postoperative]
Stage I			
Early stage breast cancer	Basic	Surgery only	
	Limited	Surgery only	Classic CMF AC, EC, or FAC
	Enhanced	Surgery only	Taxanes, Trastuzumab (HER2-positive cancers only)
	Maximal	Surgery only	Growth factors Dose-dense chemotherapy
Stage II			
Early stage breast cancer	Basic	Surgery only	Classic CMF, AC, EC, or FAC
	Limited	Surgery only	
	Enhanced	Surgery only	Taxanes, trastuzumab (HER2-positive cancers only) pertuzumab for HER2-positive cancer IF given before surgery
	Maximal	Surgery only	Growth factors Dose-dense chemotherapy
Locally advanced breast cancer (LABC)			
All stage III, those that involve the skin (T4a) or the underlying muscles of the chest (T4b) and patients with fixed axillary (armpit) lymph nodes (lymph nodes) (N2a) or infraclavicular (below the collarbone), supraclavicular (above the collarbone (N3) or internal mammary (breastbone) lymph node (N2b) involvement. Inflammatory breast cancers (IBC) are an especially aggressive presentation of LABC (T4d)	Basic	AC, EC, FAC or CMF AC, EC, FAC or CMF	AC, EC, FAC or CMF AC, EC, FAC or CMF
	Limited		
	Enhanced	Taxanes	Taxanes trastuzumab and pertuzumab (HER2-positive cancers only)
	Maximal	Growth factors Dose-dense chemotherapy	Growth factors Dose-dense chemotherapy
Metastatic disease and recurrent breast cancer (palliative)			
Systemic treatment, including chemotherapy, can only modestly extend survival. The goal of chemotherapy for metastatic breast cancer is to reduce disease-related symptoms without causing excessive treatment-related toxicities	Basic		
	Limited		Classic CMF Anthracycline monotherapy or combination
	Enhanced		Sequential single agent or combination Trastuzumab (HER2-positive cancers only) Trastuzumab plus pertuzumab T-DM1 Lapatinib
	Maximal		

Abbreviations: **CMF**, cyclophosphamide, methotrexate, and 5-fluorouracil; **AC**, doxorubicin and cyclophosphamide; **EC**, epirubicin and cyclophosphamide; **FAC**, 5-fluorouracil, doxorubicin, and cyclophosphamide.

Source: Eniu A, Carlson RW, El Saghir NS, et al. Breast Health Global Initiative Treatment Panel. Guideline implementation for breast healthcare in low- and middle-income countries: treatment resource allocation. Cancer. 2008 Oct 15;113(8 Suppl):2269-81. Updated to include recent advances in therapeutics.

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