TREATMENT:
SYSTEMIC THERAPY – CHEMOTHERAPY
FOR BREAST CANCER

About this Knowledge Summary (KS):
This Knowledge Summary is one of two Systemic Therapy Knowledge Summaries. It covers chemotherapy. The other systemic therapy KS covers hormonal therapy and targeted agents.
KEY SUMMARY

Provision of essential chemotherapy medicines
- Support availability and access to chemotherapy agents* at the basic level. The WHO includes five chemotherapy medications commonly used to treat breast cancer in the 2015 List of Essential Medicines.
- 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.
- Support availability and access to all agents required to treat chemotherapy induced side effects at the basic level (see current WHO List of Essential Medicines at www.who.int/medicines/publications/essentialmedicines/en/)

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 preoperative (neoadjuvant) 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 special 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
- Follow a defined resource-stratified pathway to maximize effective allocation of available resources and allow for coordinated incremental program improvement across the continuum of care.
  - A pathway is a progression of resource investment, program development and interval health gains.
  - Program design and improvements should be based on outcome goals, identified barriers and needs and available resources.
INTRODUCTION AND THE CHALLENGE

Chemotherapy has a central role as a breast cancer treatment modality for the majority of women with breast cancer at all resource levels. Over the past 35 years, the effectiveness of chemotherapy has increased, and, together with increased efforts in early detection, chemotherapy has contributed to major improvements in breast cancer survival. New chemotherapy formulas and the complexity of chemotherapy regimens has increased as new agents become available, new administration strategies (such as doses and timing of doses) are studied and novel regimens are identified. Studies suggest that tumor biology (which may differ among patients) affects response to chemotherapy, thus requiring tumor pathology studies prior to initiation of some treatment regimens. The toxic side-effects of chemotherapy and the resources to monitor for and manage toxicity must also be considered as part of chemotherapy treatment planning.

Studies are needed in low- and middle-income countries (LMICs) to establish best evidence-based treatment practices within these settings. Even when chemotherapy is available, many women in LMICs with breast cancer cannot afford the recommended treatments, and those who are able to afford chemotherapy often stop therapy before the treatment course 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.

POINTS FOR POLICYMAKERS

OVERVIEW

Preplanning

• Identify data sources to estimate disease burden.
• Identify who will lead the process and other stakeholders.

Planning Step 1: Where are we now? (Investigate and assess)

• Assess disease burden and availability and access to cancer medicines
• Assess workforce capacity and treatment protocols
• Identify barriers to delivery of treatment (structural, sociocultural, personal, financial)

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. Chemotherapy improves survival and 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.
• Consider implementation of a governmental policy that ensures availability of the essential chemotherapy drugs as recommended by the WHO.
• Improve capacity to safely and effectively administer available chemotherapy. This requires investing in oncology training for health professionals and recruitment and retention of medical oncologists and oncology nurses.

Planning Step 3: How do we get there? (Implement and evaluate)

• Follow a resource-stratified pathway for delivery of chemotherapy.
• Develop standard operating procedures for delivering chemotherapy that consider tumor characteristics, stage and prognosis and preferences of the patient.
• Consider treatment-related toxicities and supportive care services available to manage side-effects.
• Monitor and evaluate implementation, delivery, quality of care, access and loss-to-follow-up.
WHAT WE KNOW

Breast cancer treatment includes surgery, radiotherapy and systemic therapy. 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), as may be done for treatment of locally advanced breast cancer (LABC), postoperatively (adjuvant therapy), or for metastatic disease. Determination of the appropriate systemic therapy requires pathologic or cytologic confirmation of breast cancer, the tumor stage, and, if immunohistologic studies are available, the hormone receptor and HER2 status of the tumor (see Diagnosis: Clinical Assessment and Diagnosis: Biopsies and Pathology Studies). The recommendations for chemotherapy vary by patient-related and tumor-related factors, costs and resources availability (see Table 1).

Mechanisms of Action

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, mitotic inhibitors and topoisomerase inhibitors (less commonly used). Chemotherapy can lead to selection of chemoresistant tumor cells called clones after which an 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 chemotherapy regimens use more than one agent, as tumors may respond better to combination treatment; however, combinations may have more toxicity and require more sophisticated support systems to help patients get through their complete treatment course. Evidence-based guidelines on chemotherapy for breast cancer patients should be closely followed, and efforts must be made to confirm that the maximum number of patients complete their prescribed course.

Types of agents:

• 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).
• 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 are antitumor antibiotics that affect all phases of the cell cycle and cause cell damage and death. Anthracyclines include doxorubicin and epirubicin.
• 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.

Locally Advanced Breast Cancer (LABC)

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 other lymph node involvement. Inflammatory breast cancers (IBCs) are an especially aggressive presentation of LABC, where the breast appears inflamed but actually has tumor cells occluding the lymphatic vessels, resulting in swelling and redness. Any woman with physical 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 2 – 3 weeks, they should undergo a diagnostic work-up for cancer. Significant delays in establishing a diagnosis of IBC can worsen outcomes (see Table 2).

Patients with stage 3 LABC and IBC breast cancer are treated with preoperative chemotherapy. This will usually shrink the tumor and improve the ability of the tumor to be removed surgically. Some patients with stage IIb cancer (T3NO) are also considered to have LABC. Patients with T3N0 breast lesions may successfully undergo primary surgical resection but are often offered preoperative systemic therapy.

Preoperative (Neoadjuvant) therapy

The administration of systemic chemotherapy prior to surgical therapy can be advantageous for LABC, as it can reduce inoperable tumors to a resectable state. For larger tumors, it potentially increases 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 by chemotherapy to improve surgical options. Women with early stage breast cancer (stage I or II) may be appropriate 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.
Preoperative chemotherapy therapy options depend on the tumor subtype (see Pathology KS), the patient’s age and co-morbidities, 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. Several organizations include guidelines for chemotherapy administration, such as those outlined by the National Comprehensive Cancer Network (NCCN).

Other Systemic Preoperative and/or Postoperative Therapies

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 endocrine therapy may need to be extended compared to chemotherapy (see Systemic Therapy – Hormonal Therapy and Targeted Agents).

Special Considerations

Lymph nodes (LNs): Because preoperative therapy can impact 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 at surgery if the tumor has responded completely to the preoperative therapy. Although there is no consensus on the management of the axillary nodal beds, suspicious LNs, identified on physical exam or ultrasound, should undergo fine needle aspiration (FNA) or core needle biopsy to confirm cancer spread before preoperative therapy is administered. If a positive LN is confirmed, subsequent regional management will be needed, but will vary based on disease stage, resources and expertise availability and patient preference.

Monitoring during neoadjuvant therapy: Women receiving neoadjuvant systemic therapy should be monitored for disease progression. Generally, if there is evidence of tumor progression, the management strategy should be modified. Assessment can be done by physical exam, ultrasound, or mammography with similar levels of accuracy. If there is reduction in tumor size, treatment can proceed for up to eight cycles. At the completion of therapy, patients without inflammatory breast cancer (IBC) may be considered for breast-conserving therapy (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. Even when the tumor appears to have completely resolved based on breast examination and imaging, surgery should still be performed.

Patients with IBC 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.

Postoperative (Adjuvant) Therapy

Adjuvant 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 locoregional treatment with 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. Some of the predictive factors include the number of involved axillary lymph nodes (LNs), tumor size and histologic grade, and hormone receptor status. These variables also impact the likelihood of recurrence and death from breast cancer; adjuvant therapy should be directed toward high-risk women.

LN-positive breast cancer: In general, patients with LN-positive breast cancer should receive chemotherapy either before or after surgery.

LN-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 LN-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 chemotherapy 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 NCCN www.nccn.org).

Other Considerations

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. Patients who may not benefit from adding chemotherapy to endocrine therapy include those with small, hormone receptor-positive stage I tumors, with treatment-limiting comorbid conditions, or older ages. For women older than 70 years old, the use of chemotherapy in lymph node-negative patients has not been well established and therefore consideration should be individualized.

Adjuvant chemotherapy can be offered to women who did not complete their planned neoadjuvant course. Patients who did not respond favorably to initial neoadjuvant therapy may benefit from a non-cross-resistant chemotherapy regimen after surgery.

Patients with HER2-positive cancer should be considered for HER2-directed therapy (e.g., trastuzumab) to be given in conjunction with chemotherapy.

Patients with estrogen receptor- and/or progesterone receptor-positive cancer should receive hormonal therapy after chemotherapy completion.
Treatment of Metastatic Disease

In the majority of cases, metastatic breast cancer has a median survival of 2 years. 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. 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 its benefit compared to sequential chemotherapy is not clear. Combination chemotherapy also has higher rates of treatment-related toxicities and no proven improvement in overall survival.

The simultaneous use of endocrine therapy with chemotherapy has not demonstrated any survival advantage. Additionally, response rates for chemotherapy alone compared with endocrine therapy alone demonstrated a slight advantage for chemotherapy without a difference in overall survival. Medication selection should be based on the goals of treatment, resource availability, cost, and toxicities. Possible cytotoxic agents include an anthracycline, a taxane, capecitabine, vinorelbine, cyclophosphamide, methotrexate, gemicitabine, ixabepilone, a platinum-containing drug, 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. Mammography may pose a risk of radiation exposure to the fetus, and a lead shield should be used to protect fetus if mammography is used. Ultrasonography can be a valuable adjunct. A biopsy should be performed on any suspicious finding and should not be delayed.

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. Because pregnant women with breast cancer cannot receive radiation therapy due to risks to the fetus, BCT can only be offered if radiation can be postponed until after delivery. Anthracyline chemotherapy is safe to administer to the mother after the first trimester, because anthracyclines do not cross the placental barrier and therefore cannot reach the fetus. Tamoxifen should be avoided in pregnancy, since the mother’s hormonal regulation is important to progression of the pregnancy and may cause birth defects. Breast-feeding should be avoided in women while receiving chemotherapy, targeted agents, or hormonal therapy, since these agents might 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.

PLANNING STEP 1: WHERE ARE WE NOW?

POLICY ACTION: INVESTIGATE AND ASSESS

Assess burden of breast cancer amenable to chemotherapy

- Examine data on breast cancer stage at diagnosis.

Assess treatment protocols implementation and personnel

- National or regional guidelines for the use of chemotherapy should be available and tailored to local community 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.

Identify 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

- An assessment of cytotoxic chemotherapy should include the number and types of chemotherapeutic agents procured by the ministry of health, regulatory process and supply chain, price factors (to government and to the patient), consumption per health care facility and reported shortages and safety concerns.

Assess evaluation capacity

- Evaluate protocols, accessibility, quality of care and adherence to treatment regimens to ensure high-quality and effective treatment.
WHAT WORKS AND WHAT DOES NOT WORK

Core service requirements: 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.

Coordination of care: Chemotherapy requires a multidisciplinary coordinated team approach to minimize delays in therapy and optimize outcomes. In regions where there are shortages in medical oncologists, the use of explicit chemotherapy protocols with clear start-stop rules and flat-dosed regimens can be used to standardize chemotherapy and should include procedures and resources to manage toxic side effects. Standard protocols, including dose and regimen, 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 impact on chemotherapy tolerance and should be managed as part of a treatment plan. It is important that standard protocols consider that most studies have been performed in select high-resource settings and the results may not directly apply locally. Treatment guidelines are often resource neutral and may not be easily translatable into low-resource settings. Resource stratified treatment guidelines can help ensure appropriate chemotherapy choices (see Table 1).

Cost and effectiveness

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 women not pursuing or completing breast cancer treatments because of concerns that the cost of care will push their families further into poverty.

Health systems that follow the 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.

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. 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. In some settings, when medical oncologists are not available, non-oncologist physicians can be responsible for chemotherapy preparation and administration.

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 impact cost effectiveness, including the relative benefits of a new therapy compared to its cost 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.
HOW DO WE GET THERE?

Training and personnel: In low resource settings, medical oncologists are often not available and systemic therapy is administered by primary care physicians, surgeons or radiation therapists. 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. 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. 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.

Multidisciplinary care: Multidisciplinary teams are necessary to improve patient adherence and outcomes and should include personnel trained in medical oncology, surgery, radiation oncology, pathology and supportive care; this is particularly important with locally advanced breast cancer (LABC) when the 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.

A multidisciplinary approach supports the use of treatment guidelines across care settings and sharing of critical patient information to improve care and reduce duplication of medical efforts. Multidisciplinary teams can involve a full range of experts (surgeons, primary care clinicians and nurses, radiologists, medical oncologists, pathologists) or, in low resource settings, only two or three specially trained team members (e.g., surgeon, nurse, consulting radiologist); team members can expand as resources become available.

Improve access to care: In low-resource settings, lack of patient adherence to treatment may be caused by lack of access to care (e.g., transportation, finances) or complexity and timing of care (chemotherapy regimen that can range from once every 3 weeks for 6 months or longer). Government subsidization of public hospital charges and/or transportation may improve patient adherence. Providing community support and patient navigation may also improve patient adherence. For example, health education, advocacy, home visits and monitoring and tracking of breast cancer patients (use of mobile phone messaging) can reduce nonadherence due to lack of information and reduce loss to follow-up care due to scheduling issues.

Partnerships and collaborations: Multisectoral collaboration involving medical and patient associations, industry and other stakeholders can be engaged to help improve the availability of appropriate chemotherapy. These decisions should be based on the available efficacy data, costs, health infrastructure and community support. Multisectoral collaborations can also promote continuing medical education, the development of infrastructure for clinical trials and safety and regulatory monitoring, yet they should be pursued with appropriate ethical guidelines and oversight. International agencies and authorities address regulatory issues, such as regulations for licensing and producing cost-effective generic medicines and control generic and counterfeit medicines.
PLANNING STEP 3: 
HOW DO WE GET THERE?

POLICY ACTION: 
IMPLEMENT AND EVALUATE

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

*Bridge the gaps*
- Address gaps in the availability and safe delivery of chemotherapy.
- Strengthen formal training in medical oncology.
- Secure access to care for all populations.

*Coordinate chemotherapy and support services*
- Collaborate with academic societies, government and key stakeholders to develop guidelines and regional standards of care.
- Patients may receive chemotherapy prior to surgery or after surgery. Coordination of care between facilities can improve patient satisfaction and adherence to treatment plan. Core services include surgery, pathology laboratory, pharmacy and primary care routine evaluation and care of treatment-related toxicities.

*Monitor and evaluate*
- Anticipate, monitor and manage treatment-related toxicities.
- Document the administration and outcomes of chemotherapy 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 advancement of chemotherapy in breast cancer care is reported to contribute to a 12-21% reduction in breast cancer deaths. 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. Chemotherapy recommendations by disease stage and level of resource allocation

Breast cancer treatment includes surgery, radiotherapy and systemic therapy. Depending on the specific biologic features of a given breast cancer, systemic therapy for breast cancer can include chemotherapy, hormonal therapy and targeted agents. Several organizations include guidelines for chemotherapy administration, such as those outlined by the National Comprehensive Cancer Network (NCCN).

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Resource level</th>
<th>Prior to surgery (Neoadjuvant)</th>
<th>Post surgery (Adjuvant chemotherapy (and/or hormonal or targeted) therapy)</th>
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<tbody>
<tr>
<td>Risk factors and genetic markers can predict which patients will benefit most from specific treatments. Risk factors include axillary lymph nodes (LN), tumor size, estrogen receptor status (ER status).</td>
<td>Goal: to reduce breast cancer recurrence and to reduce inoperable tumors to a resectable state, and improve surgical options. Required for women with very large tumors to allow for successful surgery, in other stages chemotherapy may be given before or after surgery.</td>
<td>Goal: to reduce breast cancer recurrence</td>
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Stage I

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<th>Early stage breast cancer</th>
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<td>Classic CMF AC, EC, or FAC</td>
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<td>Taxanes, Trastuzumab (Her-2 positive cancers only)</td>
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<td>Growth factors Dose-dense chemotherapy</td>
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Stage II

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## Locally Advanced Breast Cancer (LABC)

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<th>Stage category</th>
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<td>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 (LNs) (N2a) or infraclavicular (below the collarbone), supraclavicular (above the collarbone (N3) or internal mammary (breastbone) LN (N2b) involvement. Inflammatory breast cancers (IBC) are an especially aggressive presentation of LABC (T4d)</td>
<td>AC, EC, FAC or CMF</td>
<td>AC, EC, FAC or CMF</td>
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## Metastatic disease & 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

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<td>Sequential single agent or combination</td>
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<td>Trastuzumab (HER2-positive cancers only)</td>
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|                            |                              |                              |                            | Trastuzumab plus pertuzumab T-DM1 Lapatinib

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


## Table 2. Locally advanced breast cancer (LABC): operable and inoperable categories

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<thead>
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<th>Operable or Inoperable</th>
<th>Stage category</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABC that may be operable at presentation</td>
<td>Stage III A: T3 with N; N2 with any T1-T3</td>
</tr>
<tr>
<td>LABC that is inoperable at presentation</td>
<td>Stage III B: T4, skin; T4b, chest wall; T4c (a+b)</td>
</tr>
<tr>
<td>Inflammatory breast cancer</td>
<td>T4d</td>
</tr>
</tbody>
</table>

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


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

- Cyclophosphamide, doxorubicin (or epirubicin), 5-fluorouracil, methotrexate, paclitaxel (or docetaxel).
KNOWLEDGE SUMMARY EARLY DETECTION MODULE (1 OF 3): BREAST AWARENESS & CLINICAL BREAST EXAM

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