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TREATMENT

Systemic Therapy: Hormonal Therapy and Targeted Agents

Knowledge Summary

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Systemic Therapy: Hormonal Therapy and Targeted Agents

INTRODUCTION

Targeted therapies have transformed the way cancer is understood and treated, and allow personalization of treatment according to each individual's tumor characteristics. Targeted cancer therapies are drugs or other substances that block the growth of cancer by interfering with specific molecules (molecular targets or receptors) that are involved in the growth, progression and spread of cancer. In the case of hormone therapies, the interaction is with estrogen receptors; in the case of human epidural growth factor 2 (HER2) targeted therapy (e.g., trastuzumab), interaction is with the HER2 receptor. Accurate testing for the presence of the estrogen receptor (ER) +/- the progesterone receptor (PR) is required for the effective use of hormonal therapy (tamoxifen, aromatase inhibitors and others) and accurate testing of HER2 receptor status is required prior to consideration of HER2 targeted therapy. While the percentage may vary by population, about two out of three breast cancers are hormone receptor positive, and one in five breast cancers are HER2 receptor positive. Hormone therapy and targeted therapies can be given as neoadjuvant (preoperative) therapy, adjuvant (postoperative) therapy and as treatment for patients with metastatic disease. Hormonal therapy can also be used as preventive therapy in select high-risk women.

Challenges include introducing and improving access to targeted agents and hormonal therapy while at the same time balancing clinical outcomes with the costs and availability of medication. Optimal targeted therapy varies by receptor status of the tumor, stage of disease, patient-related factors (e.g., comorbidities), cost and the availability as well as expertise in administering this therapy (including duration and sequencing of therapy, safety issues and toxicities). Testing for tumor biomarkers requires pathology laboratory infrastructure that may need to be established in low- or limited-resource settings. A resource-stratified pathway approach can help determine appropriate introduction of targeted therapies in a stepwise fashion (see Table 1).

KEY SUMMARY

Hormonal therapy and targeted agents for treatment of breast cancer

- Targeted cancer therapies block the growth of cancer by interfering with specific molecular targets that are involved in the growth, progression and spread of cancer.
- Many low-cost hormonal therapies, such as tamoxifen, can effectively reduce mortality from breast cancer in estrogen receptor (ER)-positive breast cancer.
- Higher-cost targeted therapies may be highly effective for selected patient populations. For example, trastuzumab, when combined with chemotherapy, can reduce mortality for women with HER2-overexpressing early-stage breast cancer by nearly 50% and significantly extend life for women with HER2-overexpressing metastatic breast cancer.

Health systems and coordination of care

- Ensure accurate receptor testing in a pathology laboratory that has appropriate equipment, trained personnel and a quality assurance program.
- Establish standardized breast cancer treatment protocols for hormonal therapy and other targeted agents to promote safe and efficient administration of therapy.
- Ensure appropriate infrastructure and training for monitoring of treatment-related patient toxicities.
- Address the availability, equitable access and processes to ensure patient adherence, especially to hormonal and other oral therapies.
- Support research to identify the most cost-effective regimens and treatment durations for each population of patients.
- Coordinated involvement of all stakeholders can identify synergies and cost-efficiencies as well as improve access to therapies.
- Cost considerations should include the infrastructure needed to deliver, monitor and manage targeted and hormonal therapies, including surveillance of toxicities.

Resource-stratified pathways across the continuum of care

- Hormonal and targeted therapies can have a significant impact on the health and survival of a woman with breast cancer. Health systems must take appropriate steps to ensure these therapies are delivered effectively and equitably.
- Follow a defined resource-stratified pathway to allow for coordinated incremental program improvement across the continuum of care (see Table 1).
- Program design and improvements should be based on outcome goals, identified barriers, needs and available resources.

POINTS FOR POLICYMAKERS:

OVERVIEW

Preplanning

- Identify data sources to estimate disease burden.
- Identify who will lead the process and stakeholders to be engaged.

Planning Step 1: Where are we now?

Investigate and assess

- Examine data and estimate the potential need for hormonal and targeted therapies and existing pathology services including the quality of diagnostic testing.
- Identify structural, sociocultural, personal and financial barriers to delivery of hormonal and targeted therapies.

Planning Step 2: Where do we want to be

Set objectives and priorities

- Establish a policy for consideration of targeted therapies as they become available.
- Identify gaps in training and expertise.
- Assess feasibility of interventions and how to balance clinical benefit to the patient, cost to the health system and equitable access to hormonal and targeted therapies.

Planning Step 3: How do we get there?

Implement and evaluate

- Invest in oncology training and recruitment and retention of medical oncologists and oncology nurses.
- Strengthen capacity to safely and effectively administer available systemic therapy.
- Follow a resource-stratified pathway to ensure prerequisites for providing hormonal and targeted therapies are established in a coordinated manner, including an assessment of existing diagnosis and treatment services available to support existing and new targeted therapies.
- Consider regulation and approval of new medications, available guidelines for appropriate use (route of administration, duration of therapy), health system infrastructure available to support therapy (including support for treatment-related toxicities) and financial burden to patient and health system.

WHAT WE KNOW

Hormone Therapy

The objective of hormone therapy is to reduce exposure of the breast cancer cells to estrogen. Many breast cancers are dependent upon estrogen and/or progesterone for growth, mediated through estrogen receptors (ER) and progesterone receptors (PR) which are expressed in about two out of three breast cancers. Hormonal agents include tamoxifen, aromatase inhibitors (AIs), fulvestrant and ovarian suppression or ablation. Tamoxifen and toremifene are selective estrogen receptor modulators (SERMs) that competitively inhibit estrogen binding to estrogen receptors with agonist and antagonist activity depending on the target tissue. SERMs can safely be administered to premenopausal and postmenopausal women. In postmenopausal women, the major source of estrogen is the conversion of androgens to estrogen by aromatase in non-ovarian tissues. Aromatase inhibitors (AIs) suppress plasma estrogen levels by inhibiting or inactivating aromatase. AIs are only appropriate therapy for postmenopausal women or premenopausal women who are concurrently receiving ovarian suppressive agents.

Receptor Testing: ER and PR testing should be performed routinely on all invasive breast cancers as soon as resources are available (see Table 1 and *Diagnosis: Biopsy, Pathology and Subtypes)*. Although ER-negative and PR-positive tumors are very uncommon, the potential benefit of endocrine therapy in treating these cancers requires that all breast cancers must be tested for both ER and PR.

Frequency of hormone positive tumors: The frequency of hormone receptor-positive tumors in a population is likely dependent on average patient age, demographic factors and tumor biology. In high-income countries, the percentage of cancers that are hormone receptor-positive is approximately 60–75% and cancers that do not express ER/PR or HER2 (called triple negative cancers) account for 15–20% of breast cancer patients. The rate of triple negative breast cancers in low- and middle-income countries (LMICs) has been reported to be as high as 40–55%. Inconsistencies and variations in populations have been attributed to poor quality of receptor testing—including improper tissue preparation and fixation—which can result in false negative ER/PR findings. As a result, the true incidence of hormone receptor-positive cancers in many regions remains unknown. The inability to accurately test for ER and PR will result in a failure to prescribe lifesaving treatment to patients with ER- or PR-positive breast cancer. In areas where hormone testing is not available, some health services prescribe hormonal patients to all patients with breast cancer. This is not recommended as women with hormone receptor-negative tumors do not benefit from hormonal therapy yet would be subjected to the toxicity and expense of ineffective therapy.

Neoadjuvant therapy

Neoadjuvant (preoperative) therapy is often administered to women with locally advanced breast cancer in an attempt to shrink the tumor and increase the likelihood of successful surgical resection. The choice of neoadjuvant endocrine therapy versus neoadjuvant chemotherapy takes into consideration drug availability and other tumor biologic characteristics as well as available health system resources (see Table 1).

Adjuvant Therapy: Hormonal

Nonmetastatic hormone receptor-positive breast cancer: The treatment plan for women with nonmetastatic hormone receptor-positive breast cancer depends on menopausal status, which must be confirmed. The *absolute* benefit from endocrine therapy relates to the risk of tumor recurrence. Overall, tamoxifen therapy has been shown to reduce the *relative* risk of recurrence by 50%. Aromatase inhibitors (AIs) have consistently shown a small reduction in breast cancer recurrence of about 3% and trend toward lower mortality of 1% compared to tamoxifen. No clear superiority of one AI over another has been demonstrated.

Premenopausal women: For women with breast cancer who were premenopausal at diagnosis, chemotherapy-induced amenorrhea is not a reliable indicator of menopausal status as ovarian estrogen production may still be present. Premenopausal women should be treated with tamoxifen monotherapy for at least 5 years. Recent studies suggest that administration for 10 years improves outcome as compared with 5 years of therapy and should be considered for women at high risk of recurrence.

Treatment timing and duration: Endocrine therapy is generally started within a few weeks after surgery for women with hormone receptor-positive breast cancer who are not receiving chemotherapy or radiotherapy. For women receiving adjuvant chemotherapy, endocrine therapy can be started after chemotherapy is completed. The timing of endocrine therapy in relation to radiotherapy does not appear to impact survival or increase the risk of treatment-related toxicities. Switching between SERMs and AIs because of treatment-related toxicities or cost concerns does not appear to impact survival or recurrence.

Metastatic Disease Management: Hormonal

Hormone therapy: The medical treatment of metastatic breast cancer depends on a patient's menopausal status and the presence and severity of symptoms, as well as tumor hormone receptor status, HER2 expression and prior exposure to endocrine therapy. A variety of hormone therapy options including SERMs (tamoxifen or toremifene), aromatase inhibitors, or fulvestrant, are available for the management of metastatic breast cancer. Treatment selection should be based on the patient and tumor charcteristics, the goals of therapy, resource availability, cost and toxicities (see Table 2). Women with

hormone receptor-positive, HER2-negative breast cancer and mild or no symptoms should initially be treated with endocrine therapy alone, rather than chemotherapy. Patients with rapidly progressive, visceral metastases, or evidence of end-organ dysfunction are often treated with chemotherapy rather than hormonal therapy as the response of the tumor to chemotherapy is more rapid than the response seen with endocrine therapy (see *Systemic Therapy: Chemotherapy for Breast Cancer*).

Premenopausal women: For premenopausal women who are endocrine therapy-naïve and present with de novo metastases, or progress greater than one year after the end of adjuvant therapy, there are several hormonal treatment options available, including ovarian suppression or ablation alone, SERMs (tamoxifen or toremifene) or AIs in combination with ovarian suppression or ablation. Megestrol acetate is an older hormonal agent that may be effective in treating metastatic breast cancer, but its use has decreased dramatically since the introduction of AIs.

Postmenopausal women: Several hormonal options also exist for postmenopausal women, including SERMs (tamoxifen or toremifene), aromatase inhibitors, or fulvestrant, which is an estrogen receptor downregulator. Some data has shown that Fulvestrant administered at higher doses may have improved survival rates compared with AIs, but it is more costly and requires intramuscular injections. Megestrol acetate is also an option.

Targeted therapies: The targeted agent palbociclib when used in combination with either fulvestrant or an AI may improve progression-free survival in women with metastatic breast cancer. This agent in combination with endocrine therapy has become a new standard for the treatment of metastatic breast cancer in some high-resouce settings but its high cost may limit its use.

Hormonal therapy side effects: Hormonal agents can cause vasomotor symptoms, mood changes, vaginal dryness and sexual dysfunction (see *Palliative Care During Treatment)*. SERMs can increase the risk of venous thromboembolic events (4 cases in 1000 women) and tamoxifen can increase the risk of endometrial cancer (4 cases in 1000 women). AIs may have a higher cardiovascular risk (8 cases in 1000 women) than SERMs, and increase rates for osteoporosis and subsequent fractures. Musculoskeletal pain due to AIs is a common reason for discontinuation.

HER2 Targeted Agents

The introduction of the anti-HER2 monoclonal antibody trastuzumab has been one of the most significant advances in breast cancer therapy. HER2 is part of a family of epidermal growth factor cell-surface receptors known as HERs or EGFRs. An increase in the abundance of HER2 on the surface of cancer cells increases the probability of receptor activation and uncontrolled cell growth. Generally, in the absence of HER2 targeted therapies, HER2-positive tumors (i.e., those that overexpress HER2) are more aggressive and associated with a worse prognosis. Several HER2-targeted agents are generally available: trastuzumab, pertuzumab (given with trastuzumab), ado-trastuzumab emtansine (T-DM1) and lapatinib. Trastuzumab has been shown to improve overall survival when used in early stage disease and progression-free survival and overall survival in metastatic disease. While it is an expensive therapy, the introduction of biosimilars may reduce costs. Dual blockage of HER2 has also been shown to be effective in metastatic breast cancer (trastuzumb plus pertuzumab). Due to its high costs, dual blockage is largely used in high income countries.

HER2-positive invasive tumors larger than 1 cm are candidates for adjuvant treatment with trastuzumab. The total recommended treatment duration with trastuzumab is 52 weeks. The addition of trastuzumab to adjuvant chemotherapy for HER2-positive tumors results in an improvement in disease-free survival, reducing the likelihood of relapse by nearly 50%. Patients with large inoperable tumors or operable tumors that otherwise would be candidates for mastectomy are candidates for targeted therapy administered in combination with chemotherpay (see *Systemic Therapy: Chemotherapy for Breast Cancer*). Patients with HER2-positive cancers treated with neoadjuvant trastuzumab or trastzumab plus pertuzumab in combination with taxane therapy have high rates of clinical response.

Receptor testing: Amplification of the HER2 gene is an adverse prognostic marker for recurrence and mortality. If anti-HER2 therapy is available, testing for HER2 overexpression should be performed. It is estimated that approximately 20% of breast tumors are HER2-positive. HER2 overexpression can be tested by immunohistochemical staining (IHC); gene amplification can be tested by fluorescence in-situ hybridization (FISH), with explicit criteria for a positive finding for each test type (see *Diagnosis: Biopsy, Pathology and Subtypes*).

Metastatic disease management

Metastatic disease management: HER2-targeted therapy can improve progression-free and overall survival for select patients with HER2-positive metastatic breast cancer. Concomitant treatment with single agent chemotherapy (usually a taxane) is common. In asymptomatic women with hormone-sensitive tumors, hormonal therapy could be given with trastuzumab. The use of additional targeted therapies (e.g., pertuzumab) depends on previous exposure to trastuzumab, disease-free interval and resource availability.

HER2-therapy side effects: HER2-targeted agents are associated with cardiac toxicities including congestive heart failure and reduced left ventricular ejection fraction (see *Palliative Care During Treatment)*. Women with previous or concurrent anthracycline use and age greater than 50 years old are at higher risk for trastuzumab-related toxicities. Surveillance for cardiac toxicities should be part of HER2-targeted therapy supportive care, including echocardiogram, if symptoms warrant and resources are available.

WHAT WORKS

Pathology services: Treatment for breast cancer can only be initiated after a pathologic diagnosis has been made. Additional testing of tumor tissue for biomarkers should inform treatment options. For example, hormone-receptor testing is required before consideration of hormonal therapy (e.g., tamoxifen), which is a low-cost, accessible medication, but it is only effective for hormone receptor-positive tumors. There is significant value in developing pathology capacity, including immunohistochemistry availability, using a resource-stratified pathway approach (see Table 1). At the basic level of resources, no pathology testing is performed beyond the diagnostic confirmation of breast cancer. Providing hormonal therapy or even surgical oophorectomy without accurate knowledge of a patient's tumor receptor status reduces the cost-effectiveness of treatment and may cause unnecessary side effects with no benefit to the patient.

Access to treatment: Efforts should be made to ensure both availability and equitable access to hormonal therapies and targeted agents—a shared responsibility of policymakers, health professionals, breast cancer experts and breast cancer advocates. Strengthening systemic treatment to include hormonal and other targeted therapies requires a collaborative approach from all invested stakeholders. There are also necessary regulatory and ethical approval processes for the introduction of any new targeted agent. This requires regulatory oversight, breast cancer expert oversight, investment in diagnosis infrastructure and health professional training and health professional and patient support. These processes should be applied consistently across all new medications. For approved agents, the cost of targeted therapy can be prohibitive, even when partial public funding is available. Therefore, novel payment models and programs to improve access to the approved targeted therapies should be considered. The quality and efficacy of all medicines, including generic drugs, must also be part of the regulatory review process. Civil society organizations and private industry should be engaged as stakeholders and potential partners to develop research programs on targeted therapy delivery and identify disparities in access to treatment.

Clinical guidelines: Evidence-based clinical practice guidelines should be followed to ensure most appropriate and up-to-date treatment strategies are employed. Timely and accurate tumor pathology is critical for effective treatment and introduction of hormonal therapies and targeted agents requires the development of standardized diagnostic and treatment guidelines to establish a minimum standard of care and the promotion of the rational use of existing resources with greater equity in access to treatment services. Treatment recommendations must consider tumor biology and local community and primary care resources, as well as patient and health professional safety issues and the availability of supportive care for short-term and long-term treatment-related side effects. Treatment regimens must be continuously evaluated for effectiveness compared with alternative agents, and be assessed for their economic impact. Strategies to evaluate and to adopt new targeted agents into clinical guidelines and routine practice should be considered.

Patient information and counseling: Patients must be informed about the benefits and risks (including long-term side effects) of targeted therapy recommendations based on appropriate diagnostic and pathology support. As an oral agent, hormonal therapies have low patient adherence to long-term therapy, with younger women being at higher risk of non-adherence. The severity of disease and therapy side effects can predict non-adherence to treatment. Patient information and counseling are needed to manage adherence.

Health professional training: In settings where there is a shortage of trained medical oncologists, the capacity of medical oncology services can be increased by permitting administration of systemic therapy by non-oncologists who have received appropriate training. They should be provided continuing medical education and evidence-based; cost-effective systemic therapy guidelines and be monitored for quality control. Training and monitoring should include safe and effective preparation and administration of all systemic therapeutics. As new therapies are approved for use, new training programs should be implemented.

Cost: The cost of targeted therapies must include the cost of pathology testing, which varies by resource setting. The current cost of trastuzumab may be prohibitive even when appropriate candidates can be identified by pathology tests. For every 1000 women with breast cancer, an estimated 200-300 will have tumors with HER2 overexpression and may benefit from treatment with trastuzumab. Trastuzumab was included on the 2015 WHO Model List of Essential Medicines. The patent expired in 2014 in Europe (2019 in USA), and biosimilar medications may soon become available at a lower cost.

Cost-effectiveness: Cost-effectiveness analysis can be useful when evaluating the relative gain achieved by introducing an additional treatment modality. The threshold of what is considered an appropriate investment varies by setting and available resources. For systemic adjuvant therapy, tamoxifen offers one of the most cost-effective interventions at approximately $1000-5000 USD per QALY. Tamoxifen is listed as a WHO essential medication, is widely available, is off patent and has an estimated median price of $0.09 USD per tablet. The cost of AIs can be significantly higher (see Appendix).

POINTS FOR POLICYMAKERS:

PLANNING STEP 1: WHERE ARE WE NOW?

Investigate and assess

Assess the Need for Targeted Therapies

- Breast cancer incidence data should include data on tumor stage and biomarkers (such as ER and HER2 status). This information is important for health system drug formulary planning.
- The frequency of hormone receptor-positive tumors in a population is likely dependent on average patient age, demographic factors and tumor biology.
- Testing for receptor status requires complex pathology analysis and quality assurance measures. Hormonal therapy and targeted agents require documentation of biomarkers to identify patients who would benefit from treatment with a particular agent.

Assess Existing Services and Treatment Plans

- National or regional treatment algorithms/guidelines should be developed to improve safety and appropriate use of hormonal and targeted therapies.
- Assess capacity for accurate high-quality laboratory testing of hormone receptor status (preanalytics, pathology services and quality control). An incorrect tumor receptor status assessment can result in administration of therapies that will not be effective and may expose the patient to unnecessary treatment-related toxicities and costs.

Assess Patient Access and Barriers to Providing Targeted Therapy

- Health system barriers may include insufficient referral processes and diagnostic capacity, lack of a reliable supply chain and skills and insufficient training of health professionals.
- Patient barriers may include cost of diagnosis and treatment, the inability to adhere to a complex and lengthy treatment plan and a lack of access to adequate management of treatment-related side effects.

Assess Health System Capacity

- Assess human resources capacity for diagnosing and testing tumor receptor status.
- Assess the regulatory and administrative processes responsible for the review, approval and implementation strategy for novel targeted agents, including price structure and negotiation, regulatory factors and supply chains, surveillance of generic or biosimilar agents and the availability of treatment protocols.

Assess Monitoring and Evaluation Capacity

- Health systems should monitor time from diagnosis to treatment as a quality metric. For example, delays in the time from biopsy to pathology assessment may indicate long biopsy specimen fixation times that can result in false negative reporting of hormone receptor and HER2 status. Delays in systemic treatment (which should be initiated within two months after surgical care) can adversely affect patient outcomes.
- Compliance to recommended treatment plan could also be monitored as a quality metric.
- Track consumption of targeted agents, provider use of treatment protocols and patient adherence to therapies when possible.

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 hormonal and targeted therapies.
- Review average patient age, demographic factors and tumor biology to estimate the frequency of hormone receptor-positive tumors in a population.

Identify gaps

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

Set achievable objectives

- Establish a process to effectively purchase and distribute hormonal and other targeted therapies, based on a resource-stratified pathway.
- Establish accurate testing of ER and PR status, with well-defined quality assurance measures.
- Develop guidelines and standards of care in collaboration with academic societies and other key stakeholders.
- Develop training for health professionals in tumor receptor testing and the administration, management and quality assurance measures for delivery of hormonal and other targeted therapies.
- Strengthen communication and coordination of services (multidisciplinary care) between health providers to improve quality and efficient delivery of care.

Set priorities and determine feasibility of interventions

- Equitable access to hormonal and other targeted therapies should be a priority, with rationale selection taking into consideration clinical benefit, the capacity to deliver quality care and full cost to the health system.
- Follow a resource-stratified pathway to ensure the prerequisites for providing targeted therapies are established in a coordinated manner, building on existing diagnosis and treatment services
- Consider cost-containment programs such as strategies to minimize drug waste.
- Consider options to minimise 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 multi-sectoral collaborations and should prioritize the WHO Model List of Essential Medicines.
- Health funding of novel targeted agents should include stakeholder consultation between governmental institutions, regulators, scientists and health professionals, industry and advocacy groups.
- Support the production of generic or biosimilar agents, which can reduce the long-term budgetary costs of targeted agents.

Implement and disseminate

- Patients should receive targeted therapies only after their eligibility is confirmed by accurate tumor receptor testing.
- Multiple treatment modalities and treatment options exist, and therefore optimal treatment requires multidisciplinary coordination of care.
- Breast cancer diagnosis and treatment are complex; coordination of care can improve patient satisfaction and adherence to planned treatment.
- Counsel health professionals on treatment protocols to ensure patients receive safe and effective therapy.
- Integration of breast cancer services at a major cancer hospital has to be counterbalanced by strengthening referral networks and reducing financial and structural health system and patient barriers to care (see *Planning: Improving Access to Care)*.
- Research priorities should be developed 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.

Monitor and evaluate

- Review biopsy procedures and pathology quality assurance programs to ensure accurate determination of hormone receptor and HER2 status.
- Novel therapies are approved based on clinical trials. Patient safety must be prioritized. Targeted agents have treatment-related toxicities that warrant surveillance.
- Quality measures include surveillance of health professional adherence to treatment protocols/guidelines for hormonal and targeted therapy as well as patient outcomes.
- 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.
- Establish assessment, process and quality metrics and outcome measures.

CONCLUSION

An improved understanding of the cellular pathways and mechanisms influencing cancer cell growth has heralded a new era of cancer treatment: targeted therapy. The pathway to breast cancer targeted therapy is inextricably linked to pathology services. Targeted therapies that are directed at over-expressed proteins or mutated signaling pathways in cancer cells allow health professionals to tailor treatment according to each individual's tumor. However, this paradigm shift has come with increased cost. Health professionals and health systems at all resource levels must develop processes to identify which medications are appropriate for their patient populations and the available health system resources, and how to optimize access to these medications. Implementation of targeted agents must be done in a coordinated manner with other advancements in breast cancer care, engaging all stakeholders from patients and advocacy groups to private industry. Policy makers and health professionals must take an active role in this process, functioning as advocates for patients and identifying cost-effective treatment options that are appropriate for each setting.

Table 1. Pharmacologic recommendations, including hormonal and targeted therapies, by disease stage and level of resource allocation

Disease stage	Basic	Limited	Enhanced	Maximal
Stage I (adjuvant)		*see footnote	Trastuzumab for treating HER2-positive disease*	
Stage II (adjuvant)		*see footnote	Trastuzumab for treating HER2-positive disease	
Locally advanced (neoadjuvant or adjuvant)		*see footnote	Trastuzumab for treating HER2-positive disease	*
Metastatic disease (stage IV) and recurrent breast cancer (palliative)	Nonopioid and opioid analgesics and symptom management	*see footnote	Trastuzumab for treating HER2-positive disease Bisphosphonates	Hematopoietic growth factors

*If the costs associated with trastuzumab were substantially lower, trastuzumab would be used at a limited level. In this case, measurement of HER2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER2/neu targeted biological therapy. NOTE: Trastuzumab is on the 2015 WHO List of Essential Medications.

Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited and enhanced levels settings.

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.

Table 2. Primary neoadjuvant hormone therapy in locally advanced breast cancer

Primary Neoadjuvant Hormone Therapy
Tamoxifen produces variable clinical response rates.
Tamoxifen allows breast conservation rates in up to 35% of patients.
AIs produce more clinical responses than tamoxifen, up to 55%.
AIs allow more breast-conserving surgery than tamoxifen: up to 45% of patients.
The role and duration of preoperative hormone therapy remains undefined.
Hormone therapy may be justified as PST in elderly patients with a known positive hormone-receptor status or slow-growing tumors with an unknown receptor status.
Hormone therapy rarely produces complete pathologic remission.
Tamoxifen may be justified in those situations in low-resource settings. AIs are more effective than tamoxifen and are used in enhanced and maximal resource settings .
Chemotherapy is the first choice in inoperable, locally advanced breast cancer.
Hormone therapy should be given after surgery for hormone-responsive tumors in accordance with adjuvant therapy recommendations and durations at all levels of resources.

Abbreviations: **AIs**, aromatase inhibitors; **PST**, primary systemic therapy; **LABC**, locally advanced breast cancer.

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.

Table 3. Therapy overview: adjuvant hormonal therapy

	Strengths	Weaknesses	Required Resources
Adjuvant hormonal therapy	Adjuvant hormonal therapy in women with ER-or PR- positive or unknown breast cancer substantially. reduces the risk of disease recurrence and death Limited toxicity Easily administered by general practitioner or surgeon Benefits increase with increasing risk of recurrence	Optimally requires availability of ER and PR status determination Benefits are limited in low-risk breast cancer Compliance varies	Pathology. Tumor steroid hormone receptor content Number of involved axillary lymph nodes Tumor size Tumor histologic grade Resources for management of toxicities Pharmacy/drug distribution
Specific adjuvant endocrine therapies			
Tamoxifen	Improves disease-free and overall survival in all age groups and nodal status subsets and with or without chemotherapy in ER- and PR+ or unknown breast cancers Reduces risk of second, contralateral breast cancers Appears to maintain bone mineral density in postmenopausal women Inexpensive Known long-term toxicity profile	Toxicity side effects: hot flashes, thromboembolic disease, endometrial carcinoma, cataracts	Same as for adjuvant endocrine therapy (see above); resources for management of toxicities should include gynecologic resources
Aromatase inhibitors	In postmenopausal women with hormone receptor positive resected breast cancer Anastrozole is superior to tamoxifen Anastrozole or exemestane sequentially with 2-3 years of tamoxifen is superior to tamoxifen alone Extended therapy with letrozole following 4.5-6 years of tamoxifen is superior to 5 years of tamoxifen alone There is no increase in thromboembolic events or endometrial cancer	Absolute difference between aromatase inhibitors and tamoxifen alone in terms of disease-free survival is uncertain Impact on survival is uncertain Substantially higher cost or aromatase inhibitors compared with tamoxifen alone Toxicity: increased risk of bone fracture, arthralgia	Same as for adjuvant endocrine therapy (see above)
Ovarian ablation	Effective therapy in the treatment of breast cancer in premenopausal women with ER- and PR- positive or unknown breast cancer Equivalent to CMF chemotherapy Oophorectomy plus tamoxifen may be considered an appropriate adjuvant hormonal therapy	Long-term adverse effects of estrogen deprivation in young women High cost if LH-RH agonist used	Core surgical resource* Pathology (see general above) Resources for management of toxicities

*See Diagnosis: Biopsy, Pathology and Subtypes.

**See Locoregional Therapy: Surgery for Breast Cancer.

CMF, cyclophosphamide, methotrexate and 5-fluorouracil; **ER**, estrogen receptor; **LH-RH**, luteinizing hormone-releasing hormone; **PR**, progesterone receptor.

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.

APPENDIX

Table A1. HER2 testing

	Basic	Limited	Enhanced	Maximum
Should HER2 testing be done?	No	No	Yes	Yes
Should HER2 testing be done for DCIS?	NA	NA*	No	No
Should FISH be done for upfront HER2 testing?	NA	NA*	No	Yes†
Should FISH be done for HC equivocal cases?	NA	NA*	Yes	Yes
Should reporting of results follow ASCO-CAP guidelines?	NA	NA*	Yes	Yes

HER2=human epidermal growth-factor receptor type 2. **DCIS**=ductal carcinoma-in-situ. **NA**=not applicable. **FISH**=fluorescent in-situ hybridisation. **IHC**=immunohistochemistry. **ASCO**=American Society of Clinical Oncology. **CAP**=College of American Pathologists. *If a tiered private health-care system exists, follow consensus as for enhanced level of resources. †Can be considered as an alternative to upfront HER2 testing by immunohistochemistry.

Table 1: Consensus for HER2 testing based on level of health care resources

Source: Wong NS, Anderson BO, Khoo KS, et al, Asian Oncology Summit. Management of HER2-positive breast cancer in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol. 2009 Nov;10(11):1077-85.

Table A2. HER2 targeted therapy

	Basic	Limited	Enhanced	Maximum
Inclusion criteria for anti-HER2 targeted therapy by FISH testing	NA	NA*	FISH HER2:17CEP ratio >2.0	FISH HER2:17CEP ratio >2.0
Can adjuvant trastuzumab be offered?	No	NO* Consider Tra+P for 3 months followed by anthracyclines	Yes	Yes
Should preoperative systemic therapy include trastuzumab?	No	No*	Yes	Yes
Threshold tumour size for adjuvant trastuzumab (lymph node NA negative)	NA	NA*	>1 Cm	>1 cm (>0-5 cm ifER negative and grade 3, or LVI positive, Orage <35years)†
Optimum duration of adjuvant trastuzumab	NA	NA*	1 year	1 year
Trastuzumab scheduling with chemotherapy	NA	NA*	Concurrent or sequential	Concurrent or sequential
Should adjuvant trastuzumab (with or without endocrine therapy) be offered in the absence of chemotherapy?	NA	NA*	No	Non-evidence-based option
Threshold tumour size for adjuvant chemotherapy (lymph node negative)	>2 Cm	>1 Cm	>1 Cm	>1 cm (>0-5 cm if ER negative and grade 3, or LVI positive, or age <35years)
Preferred adjuvant chemotherapy	CMF, CAF, or FAC	CAF or FAC	CAF or FAC followed by Tra; CEF or FEC followed by Tra; AC followed by Por D with Tra; DCarb with Tra; DC with Tra	CAF or FAC followed by Tra; CEF or FEC followed by Tra; AC followed by Por D withTra; DCarb WithTra; DC WithTra
Preferred endocrine therapy	Tamoxifen (consider oophorectomy if premenopausal)	Tamoxifen (consider oophorectomy if premenopausal)	Tamoxifen (premenopausal) aromatase inhibitors (postmenopausal)	Tamoxifen (premenopausal) aromatase inhibitors (postmenopausal)
Should adjuvant lapatinib be used?	NA	NA*	No‡	No‡

HER2=human epidermal growth-factor receptor type 2. **FISH**=fluorescent in-situ hybridisation. **NA**=not applicable. **17CEP**=17 centromere enumerating protein. **Tra**=trastuzumab. **P**=paclitaxel. **ER**=estrogen receptor. **LVI**=lymphovascular invasion. **C**=cyclophosphamide. **M**=methotrexate. **F**=fluorouracil. **A**=doxorubicin (adriamycin). **E**=epirubicin. **D**=docetaxel. **Carb**=carboplatin. *If a tiered private health care system exists, follow consensus as for enhanced level of resources. †Non-evidenced-based and controversial. ‡Pending data from randomised trials.

Table 2: Consensus for management of HER2-positive early breast cancer based on level of health-care resources. **Source:** Wong NS, Anderson BO, Khoo KS, et al, Asian Oncology Summit. Management of HER2-positive breast cancer in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol. 2009 Nov;10(11):1077-85.

Table A3. Palliative use of trastuzumab

	Basic	Limited	Enhanced	Maximum
Can palliative trastuzumab be offered?	No	No*	Yes	Yes
Should maintenance anti-HER2 targeted therapy be continued beyond maximum tumour response?	NA	NA*	Yes	Yes
Should trastuzumab be continued beyond disease progression?	NA	NA*	Yes	Yes
Should trastuzumab be given concurrently with, or sequentially before, chemotherapy?	NA	NA*	Individualised	Individualised
Can capecitabine plus lapatinib be offered after progression on anthracyclines, taxanes, and trastuzumab?	NA	NA*	Yes	Yes
Can combination capecitabine and lapatinib be offered for CNS disease progressing after WBRT and prior trastuzumab-based treatment?	No	No	Yes	Yes
Should trastuzumab be combined with AIs in postmenopausal women with endocrine responsive HER2-positive advanced disease?	NA	NA*	Yes	Yes
What is the role of T-DM1, everolimus, HSP inhibitors, and bevacizumab?	Clinical trials if resources available	Clinical trials	Clinical trials	Clinical trials

HER2=human epidermal growth-factor receptor type 2. **NA**=not applicable. **WBRT**=whole-brain radiotherapy. **AI**=aromatase inhibitors. **T-DM1**=trastuzumab-DM1 antibody-drug conjugate. **HSP**=heat-shock protein. *If a tiered private healthcare system exists, follow consensus as for enhanced level. **Table 3:** Consensus for management of HER2-positive advanced breast cancer based on level of health-care resources. **Source:** Wong NS, Anderson BO, Khoo KS, et al, Asian Oncology Summit. Management of HER2-positive breast cancer in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol. 2009 Nov;10(11):1077-85.

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