EARLY STAGE BREAST CANCER

Executive Summary

Early stage breast cancer is defined as disease confined to the breast with or without regional lymph node involvement, and the absence of distant metastatic disease. This is based on the fact that early-stage breast cancer is potentially curable, and patients with distant metastatic disease are not. In developed countries more than 80% of patients with early-stage breast cancer have long-term survival after surgery, and in some cases systemic therapy such as chemotherapy, hormone therapy, and targeted therapy, and local radiation.[1] By contrast, breast cancer patients with distant metastases are rarely long-term survivors.

Treatment of early-stage breast cancer always includes surgical removal of the breast tumor and removal of some axillary lymph nodes. Surgery alone will result in long-term survival for some patients. Systemic therapy and local radiation can significantly improve the chances for long-term survival, depending on the stage of disease, and biologic subtype of breast cancer. Therefore, the benefit of systemic therapy should be viewed as incremental benefit above surgery alone.[2-5] Systemic therapy includes hormone therapy (tamoxifen and aromatase inhibitors), chemotherapy, and targeted therapy such as trastuzumab.

Breast cancer is no longer viewed as a single disease, but rather as a series of diseases defined by biologic characteristics based on hormone receptor status and HER2 status. Tumors positive for either estrogen or progesterone receptor can be considered hormone receptor (HR) positive. Breast cancer can be viewed as 4 sub-types, as follows: 1) HR positive/HER2 negative, 2) HR positive/HER2 positive, 3)HR negative/HER2 positive, 4) HR negative/HER2 negative. These biologic sub-types determine which therapies will have potential efficacy. Hormone therapy is beneficial only for patients with HR positive tumors, and trastuzumab and similar HER2 targeted therapies are only helpful in women with HER2 positive cancers.

For many patients, surgical removal of the primary breast tumor and axillary node sampling is the first procedure, followed by systemic therapy and radiation if indicated. In these circumstances, patients can be treated either with modified radical mastectomy or lumpectomy. In patients who undergo lumpectomy, it is critical for the cancer to be completely removed with negative margins on pathologic assessment, and these patients should always receive whole-breast radiation. Patients treated with mastectomy will benefit from post-mastectomy radiation if they have extensive breast tumors or involved axillary lymph nodes.[6,7]

Locally advanced disease is where the cancer is still confined to the breast and regional lymph nodes, but is extensive precluding initial surgical resection. Large tumors, tumors that are attached to skin or underlying chest wall structures, or those with extensive axillary involvement often quality as factors denoting locally advanced disease. These patients are often treated with systemic therapy prior to surgery, and if there is adequate response to therapy, they can then

undergo surgical resection of their cancer. Locally advanced disease is seen more commonly in the developing world than in developed countries.[8]

Public Health Relevance

Breast cancer comprises one-quarter of all new cancer cases worldwide including women and men, with an estimated 1.67 million cases in 2012 alone, according to the International Agency for Research on Cancer (IARC). Although highly treatable with systemic therapy, surgery, and radiation therapy (as described in the present briefing), breast cancer was the cause of death of approximately half a million women worldwide in 2012.[9] In sub-Saharan Africa alone, it is believed that nearly 50,000 women passed away from the disease during that one year. The ratio of incidence to mortality in high-income, middle-income, and low-income countries varies drastically given the disparities in access to resources, clinical knowledge, and medicines, as is true for all cancers. According to one study in 2010, the 5-year survival rate for breast cancer ranged from 12% survival in The Gambia, an extremely poor country, to 79% in South Korea, a high-income country.[10] As El Saghir and colleagues noted in their 2011 article in *The Breast*, women suffering from breast cancer in the developing world are more likely to present at later stages to a health facility due to structural barriers to care, absence of treatment options, or inadequate information being disseminated to the public.[11] Women who receive treatment for early stage breast cancer (localized disease) have a significantly higher chance of survival than those treated for metastatic disease. Even in less developed regions of the world, such as Costa Rica, India, Philippines, Saudi Arabia, and Thailand, overall survival at 5 years for women treated for localized disease was 73.6% on average, compared to 47.4% with regional disease.[10] There are several major global initiatives focusing on implementation of breast cancer guidelines, including the Breast Health Global Initiative, which has developed a set of guidelines for public sector development of national responses to the disease.[12,13]]

Requirements for diagnosis, treatment, and monitoring

Diagnostics:

The treatment of breast cancer should always be determined by pathology evaluation of the primary cancer. Biopsy is often performed by ultrasound-guided core needle technique, though incisional biopsy is sometimes performed. Fine needle aspirate can play a role but cannot distinguish between in-site and invasive cancer and often does not give adequate material for immunohistochemistry. Evaluation of the biopsy by an experienced pathologist will yield the histologic subtype (ductal, lobular, etc.) and grade of the cancer. Immunohistochemistry (IHC) analysis for estrogen receptor, and in some cases progesterone receptor is critical since this will determine whether the cancer is potentially sensitive to hormone therapy. HER2 can be assessed by either IHC or by fluorescene in situ hybridization (FISH), and is critical to determine whether the cancer might be sensitive to HER2 directed targeted therapy with agents such as trastuzumab.

Evaluation of surgical specimens, either lumpectomy or mastectomy should include pathology confirmation of histology as well as assessment of surgical margins. Evaluation of axillary lymph nodes should record total number of nodes resected, and total number of nodes involved with cancer.

Testing:

It is important to determine whether the primary breast tumor is resectable or not. Generally involvement of the skin and/or chest wall structures are signs that resection are not likely to be successful. Breast ultrasound can help to determine this, though physical exam is very helpful. Metastatic disease should be ruled out, preferably with CT scans and a bone scan. When these are not available, chest x-ray and liver ultrasound can give important information. CBC, liver function tests, electrolytes and renal function testing are all essential to determine fitness to undergo both surgery and systemic therapies.

Administration and Care of Patients:

Hormone therapies are largely oral (tamoxifen and aromatase inhibitors). No special testing or administrative resources are necessary for the utilization of these drugs, though a reliable supply is important.

Cytotoxic chemotherapy requires the ability to administer intravenous chemotherapy, with particular consideration of avoidance of extravasation with doxorubicin, and allergic reactions with taxanes. Chemotherapy can be administered in an out-patient infusion setting, or an in-patient setting, though this is not required. IV fluids and anti-emetics as well as hypersensitivity medications are required. Monitoring of CBC, renal function, electrolytes and liver functions tests are required.

Trastuzumab and similar anti-HER2 targeted therapies are generally administered intravenously. Administration is relatively straightforward, and is usually done in out-patient infusion facilities.

Cardiac monitoring is recommended for patients receiving an anthracycline and/or trastuzumab, though the incidence of serious cardiac toxicity is low, and in most cases reversible, and the potential benefit in disease control is substantially increased with utilization of these agents in patients with HER2 positive disease. [14,15]

As with all cancer treatment, social support, clean water and adequate nutrition are essential.

Overview of Regimens

The following tables include basic information on administration and dosing for the 4 biologic subtypes of breast cancer, followed by specific regimens.

1) HR Positive/HER2 Negative tumors

Except for the very smallest tumors with negative axillary nodes, adjuvant hormonal therapy should always be administered. For decades 5 years of therapy was considered standard, though 2 recent studies have shown small additional benefit for 10 years of hormonal therapy.[2] Tamoxifen has been shown to reduce systemic recurrence rates by 50%.[16] For post-menopausal patients use of aromatase inhibitors in place of tamoxifen, or after a course of tamoxifen had a small incremental benefit for reducing distant recurrences, though only a marginal benefit for overall survival. When chemotherapy is administered, hormone therapy should always be initiated after the completion of chemotherapy. HER2 directed agents and hormone therapy can be given concurrently.

Chemotherapy will add to benefit particularly for women with large cancers and involved axillary lymph nodes.

For patients with locally advanced cancer requiring pre-operative (neo-adjuvant) therapy, chemotherapy is usually the treatment of choice, though hormone therapy can be used in place of chemotherapy.

2) HR Positive/HER2 Positive tumors

As above, hormone therapy should always be a component of the therapy for these patients.

Chemotherapy plus trastuzumab should be administered to all patients but those with very small, node negative tumors (< 0.5 cm). Typically trastuzumab is given concurrently with a taxane, and not administered concurrently with an anthracycline. Trastuzumab should be administered for a year. For patients receiving pre-operative therapy the combination of a taxane, trastuzumab and pertuzumab has been shown to be more effective than a taxane and trastuzumab alone. The addition of pertuzumab as part of post-operative adjuvant therapy has not been shown to be beneficial. The role of T-DM1 as adjuvant therapy remains undefined.

3) HR Negative/HER2 Positive tumors

Hormone therapy is not indicated. Trastuzumab chemotherapy combinations as described in #2 are indicated.

4) HR Negative/HER2 Negative tumors

Hormone therapies, and trastuzumab containing regimens are not indicated for these patients. Chemotherapy regimens are listed below.

Standard Chemotherapy Regimens (non-trastuzumab regimens)

AC – Doxorubicin and Cyclophosphamide (4 cycles) (for sub-types 1, 4 – and 2, 3 if trastuzumab not available)

Doxorubicin	*IV*	*60 mg/m²*	
Cyclophosphamide	*IV*	*600 mg/m²*	*q 3 weeks x 4 cycles*

AC-T – Doxorubicin/Cyclophosphamide followed by paclitaxel (4 cycles of each) (for sub-types 1, 4 – and 2, 3 if trastuzumab not available)

Doxorubicin	*IV*	*60 mg/m2*	
Cyclophosphamide	*IV*	*600 mg/m2*	*q 3 weeks x 4 cycles*

Followed by

Paclitaxel	*IV*	*175 mg/m²*	*q 3 weeks x 4 cycles*
Or			
Paclitaxel	*IV*	*80 mg/m²*	*q 1 week x 12 weeks*
Or			
Docetaxel	*IV*	*100 mg/m²*	*q 3 weeks x 4 cycles*

Note: For paclitaxel the q 1 week schedule is superior to the q 3 week schedule and should be utilized unless the patient is not able to come for weekly treatment

TC – Docetaxel/Cyclophosphamide (4 cycles) (for sub-types 1, 4 – and 2, 3 if trastuzumab not available)

Cyclophosphamide	*IV*	*600 mg/m²*	
Docetaxel	*IV*	*75 mg/m²*	*q 3 weeks x 4 cycles*

Oral CMF (Every 28 days for 6 cycles)

Cyclophosphamide	*PO*	*100 mg/m²*	*Daily, days 1-14*
Methotrexate	*IV*	*40 mg/m²*	*Days 1 and 8*
5-FU	*IV*	*600 mg/m²*	*Days 1 and 8*

Alternative Regimen (if other regimens above are not available)

FAC

5-FU	*IV*	*500 mg/m²*	
Doxorubicin	*IV*	*50 mg/m²*	
Cyclophosphamide	*IV*	*500 mg/m²*	*q 3 weeks x 6 cycles*

Standard Regimens Including Trastuzumab, for HER2 Positive disease

AC-TH – Doxorubicin/Cyclophosphamide followed by paclitaxel/trastuzumab (for sub-types 2,3)

Doxorubicin	*IV*	*60 mg/m^2*	
Cyclophosphamide	*IV*	*600 mg/m^2*	*q 3 weeks x 4 cycles*
Followed by			
Paclitaxel	*IV*	*80 mg/m2*	*q 1 week x 12 weeks*
*Trastuzumab**	*IV*	*2 mg/kg*	*q 1 week x 12 weeks*
Or			
Docetaxel	*IV*	*100mg/m2*	*q 3 weeks x 4 cycles*
*Trastuzumab**	*IV*	*2 mg/kg*	*q 1 week x 12 weeks*
Followed by			
Trastuzumab	*IV*	*6 mg/kg*	*q 3 wks to finish 1 yr of therapy*

**loading dose first week of therapy trastuzumab 4 mg/kg (alternatively, trastuzumab can be used every 3 weeks with an 8 mg/kg bolus and maintenance of 6mg/kg every 3 weeks)*

TCH – Docetaxel/Carboplatin/Trastuzumab (for sub-types 2,3)

Docetaxel	*IV*	*75 mg/m2*	
Carboplatin	*IV*	*AUC = 6*	
*Trastuzumab**	*IV*	*6 mg/kg*	*q 3 wks x 6 cycles*
Followed by			
Trastuzumab	*IV*	*6 mg/kg*	*q 3 wks to complete 1 yr of therapy*

**First dose of trastuzumab loading dose 8 mg/kg*

Note: Epirubicin can be substituted for doxorubicin at an equipotent dose, and is recommended to be included in the EML as a class agent with doxorubicin for treatment of breast cancer.

Standard Hormone Regimens (premenopausal and postmenopausal women)

Tamoxifen	Oral	20 mg/day	*x 5 years**

Standard regimen for postmenopausal women who have contraindications to or are intolerant to tamoxifen

Anastrozole	Oral	1 mg/day	*x 5 years**

Note: it is recommended that anastrozole be added to the EML as a class agent for aromatase inhibitors and that in this class letrozole and exemestane be included.

Premenopausal women should receive tamoxifen for at least 5 years. There is a small benefit for treatment for 10 years compared to 5 years. For premenopausal women who have an absolute contraindication to tamoxifen or are intolerant of tamoxifen, ovarian suppression by surgery, radiation, or medication in combination with an aromatase inhibitor is an acceptable alternative.

Postmenopausal women can be treated with 5 years of an aromatase inhibitor, or 2-3 years of tamoxifen followed by an aromatase inhibitor to complete 5 years. Alternatively, a patient can be treated with 5 years of tamoxifen followed by 5 years of an aromatase inhibitor. There is a small benefit for treatment for 10 years compared to 5 years. If aromatase inhibitors are not available or if the patient is intolerant of an aromatase inhibitor, treatment with tamoxifen for the entire course is acceptable. There is a small benefit to disease-free survival, and marginal benefit to overall survival for use of an aromatase inhibitor in the treatment course. A meta-analysis demonstrated an absolute decrease in recurrence of 3.1% on AIs as compared to tamoxifen (5.0% versus 8.1%), and an absolute decrease in breast cancer mortality of 0.7% (1.7% versus 2.4%).[22]

Review of Benefits and Harms

Benefits

Surgery will cure some patients with early-stage breast cancer without additional adjuvant therapy, however the chance for cure with surgery alone depends on tumor size, grade, axillary node involvement and biologic sub-type. Adjuvant hormonal and systemic therapy reduces the incidence of recurrent metastatic breast cancer in patients who present with early-stage breast cancer. Since those patients who develop metastatic breast cancer almost always die of their disease, reducing the odds of systemic relapse greatly improves survival.

Hormone therapy reduces the risk of systemic recurrence by 50% though the absolute benefit relates to the overall risk of relapse which relates to tumor size, grade, and axillary nodal involvement. The improvement in relapse-free survival with chemotherapy varied by biologic sub-type as well as overall risk of relapse, again based on tumor size, grade and axillary nodal status.

For patients with HER2 positive disease, the addition of trastuzumab to chemotherapy further reduces the risk of relapse significantly over chemotherapy alone. The study with the longest follow-up as of 2014 concluded that at 10 years overall survival rate increased from 75.2-84.0% (HR 0.63).[21] In addition, the addition of trastuzumab to chemotherapy as pre-operative therapy for locally advanced disease dramatically increases the response rate.

Harms and Toxicity Considerations

Common
Risks of treatment include common short-term toxicities such as alopecia, neutropenia, fever and infection, and neuropathy (ranging 15-60%) from taxanes. Paclitaxel and trastuzumab are associated with infusion reactions in up to 30-40% of patients, most reactions are mild and easily managed.[17,18]

Tamoxifen can cause hot flashes, mood changes, and rarely thromboembolic disease and endometrial cancer. Tamoxifen generally has a positive effect on bone density. Aromatase inhibitors can cause hot flashes, mood changes, musculoskeletal complaints and bone loss.

Serious
Cardiac muscle suppression or damage can occur after therapy with anthracyclines and trastuzumab and administration of both agents together increases the risk. For the regimens described above, the risk of congestive heart failure is small and reversible upon discontinuation in most cases.[15,19,20]

Rare incidences of bone marrow damage, myelodysplastic syndrome and acute leukemia can occur after therapy with cyclophosphamide and doxorubicin.

Systematic Reviews and Major Trials

The following reviews and analyses summarize the literature supporting the treatment regimens for early stage breast cancer.

EBCTCG, 2012. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *The Lancet*, 379(9814), pp.432–444.

Summary: CMF and 4AC regimens reduce 10-year breast cancer-related mortality by roughly one third when compare with no chemotherapy, a finding that is largely independent of other factors. A further 15-25% reduction in breast cancer-related mortality can be achieved using 4AC + 4 cycles of Paclitaxel given three times weekly.

Burstein, H.J. et al., 2014. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J Clin Oncol*, 32(21), pp.2255–2269.

Summary: Systematic review of recent trials (Jan 2009 – Jan 2013) and analysis of three historical trials, now recommend that for hormone-receptor positive breast cancer, if women have received 5 years adjuvant tamoxifen, offer choice of continuing tamoxifen or switching to AI for 10 years total adjuvant endocrine therapy.

Davies, C. et al., 2013. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS,a randomised trial. *The Lancet*, 381(9869), pp.805–816.

Summary: Absolute mortality reduction of 2.8% for women who continued on tamoxifen for 10 years compared to those who stopped at 5 years (12.2% vs 15.0% mortality risk) for patients with ER+ breast cancer.

Cuzick, J. et al., 2010. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *The lancet oncology*, 11(12), pp.1135–1141.

Summary: Anastrozole alone improved 3-year disease-free survival compared with tamoxifen (89% vs 87%) or combination (87%) in ER+, post-menopausal patients.

Goss, P.E. et al., 2003. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *NEJM.* 349(19), pp.1793–1802.

Summary: Addition of letrozole 2.5mg (AI) to adjuvant tamoxifen x 5 years improved 4-year disease-free survival by 6% (87 -> 93%) for post-menopausal women.

Giordano, S.H. et al., 2014. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*, 32(19), pp.2078–2099.

Summary: HER-2 targeted therapy (trastuzumab, pertuzumab) is recommended as first line therapy for all patients with HER-2 receptor positive breast cancer except: 1) selected patients with low risk ER or PR positive and HER-2 positive breast cancer where endocrine therapy alone is sufficient; 2) patients with clinical CHF or very low LVEF, who should be evaluated on a case-by-case basis. Duration of 4 to 6 months, or until maximum response.

Moja, L. et al., 2012. *Trastuzumab containing regimens for early breast cancer (Review)*, The Cochrane Collaboration.

Summary: Meta-analysis of 8 trials, 11,991 patients. Combined HR for both overall survival and disease-free survival significantly support addition of trastuzumab (HR 0.66; 0.60; respectively). Significantly increased risk of congestive heart failure, left ventricular ejection fraction decline (RR: 5.11; 1.83 respectively), but benefit far outweighs risk in patients with high risk of recurrence, healthy heart.

Recommendations

The reviewers recommend the incorporation of early stage breast cancer treatment options into the WHO Model List of Essential Medicines, and recommend specifically that trastuzumab and anastrozole (as a class including aromatase inhibitors) be added to the core Essential Medicines List.

Standard Regimen
Chemotherapy regimen
Trastuzumab for HER2-positive
Hormone therapy for HR-positive

Acceptable Alternative when trastuzumab not available
Chemotherapy regimen
Hormone therapy for HR-positive

Additions proposed for Section 8.2 of the EML

Trastuzumab
Anastrozole (to be added to the EML as a class agent to include letrozole and exemestane)

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