Early-stage breast cancer – EML

The application sought the inclusion of treatment options for early-stage breast cancer on the core list of the EML and proposed that trastuzumab and anastrozole (representing the therapeutic class of aromatase inhibitors) be added to the Model List. Medicines proposed for the treatment of early-stage breast cancer already included on the Model List include doxorubicin, cyclophosphamide, paclitaxel, docetaxel, methotrexate, 5-fluorouracil, carboplatin and tamoxifen.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Early-stage breast cancer is defined as disease confined to the breast, with or without regional lymph node involvement, in the absence of distant metastatic disease. This is based on the fact that early-stage breast cancer is potentially curable, while distant metastatic disease is not. In developed countries, more than 80% of patients with early-stage breast cancer have long-term survival after surgery, and in some cases with systemic therapy such as chemotherapy, hormone therapy, 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 tumour and 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 the molecular subtype of breast cancer. Systemic therapy should therefore be viewed as providing incremental benefit beyond surgery alone *(2-5)*. Systemic therapy includes hormone therapy (tamoxifen and aromatase inhibitors), chemotherapy, and targeted therapy such as trastuzumab.

Breast cancer can be viewed as four subtypes, as follows:

1. Hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative
2. HR-positive/HER2-positive
3. HR-negative/HER2-positive
4. HR-negative/HER2-negative.

These molecular subtypes determine which therapies are likely to be efficacious. Hormone therapy is beneficial only for patients with HR-positive tumours, and trastuzumab and similar HER2-targeted therapies are helpful only in women with HER2-positive cancers.

For many patients, surgical removal of the primary breast tumour 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 pathological 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 tumours or involved axillary lymph nodes *(6, 7)*.

Locally advanced disease refers to a cancer that is still confined to the breast and regional lymph nodes but is sufficiently extensive to preclude initial surgical resection. Large tumours, tumours that are attached to skin or underlying chest wall structures, and those with extensive axillary involvement often qualify as denoting locally advanced disease. Patients with locally advanced disease are often treated with systemic therapy before surgery and, if response to therapy is adequate, can then undergo surgical resection of the 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 in women and men worldwide, with an estimated 1.67 million cases in 2012 alone, according to GLOBOCAN 2012, the database of the International Agency for Research on Cancer. Although highly treatable with systemic therapy, surgery and radiation therapy, 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 died from the disease during that one year. The ratio of incidence to mortality in high-, middle- and low-income countries varies dramatically, reflecting disparities in access to resources, clinical knowledge and medicines (as is the case for all cancers). According to one study in 2010, the 5-year survival rate for breast cancer ranged from 12% in Gambia, an extremely poor country, to 79% in the Republic of Korea, a high-income country *(10)*. It has been noted that women suffering from breast cancer in the developing world are more likely to present to health facilities at later stages because of 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 with 47.4% for women with regional disease *(10)*.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

The treatment of breast cancer should always be determined by pathological evaluation of the primary cancer. Biopsy is often performed by ultrasound-guided core needle technique, although incisional biopsy is useful to distinguish between in-situ and invasive cancer. Fine-needle aspiration can play a role but does not allow a distinction between in-situ and invasive cancer and often does not give adequate material for immunohistochemistry. Evaluation of the biopsy by an experienced pathologist will yield the molecular subtype and grade of the cancer. Immunohistochemistry (IHC) analysis for estrogen receptors, and in some cases progesterone receptors, is critical since this will determine whether the cancer is potentially sensitive to hormone therapy. HER2 can be assessed either by IHC, or by fluorescence in situ hybridization (FISH) if IHC is equivocal, and is critical to determine whether the cancer might be sensitive to HER2-targeted therapy with agents such as trastuzumab.

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

Testing

It is important to determine whether the primary breast tumour is resectable or not. Generally, involvement of the skin and/or chest wall structures indicates that resection is unlikely to be successful. Breast ultrasound can help to determine this, although physical examination is very helpful. Metastatic disease should be ruled out, preferably with computerized tomography scans and a bone scan. When these are not available, chest X-ray and liver ultrasound can give important information. Complete blood count (CBC), liver function tests, electrolytes and renal function testing are all essential to determine a patient's fitness to undergo both surgery and systemic therapies.

Administration and care of patients

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

Cytotoxic chemotherapy requires the ability to administer intravenous chemotherapy, with particular consideration of avoidance of extravasation with doxorubicin and of allergic reactions with taxanes. Chemotherapy can be administered in an outpatient infusion setting or an inpatient setting, although this is not required. Intravenous fluids and

antiemetics are required and hypersensitivity medications must be available. 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 outpatient infusion facilities.

Cardiac monitoring is recommended for patients receiving trastuzumab or an anthracycline, although the incidence of serious cardiac toxicity is low – and in most cases reversible – and the potential benefit in disease control is substantially increased with use of these agents in patients with HER2-positive disease *(12, 13)*.

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

Overview of regimens

The following provides basic information on administration and dosing for the four molecular subtypes of breast cancer, followed by specific regimens.

HR-positive/HER2-negative tumours

Tamoxifen has been shown to reduce systemic recurrence rates by 50% *(2)*. For decades, five years of therapy was considered standard, although recent studies have shown a small additional benefit for 10 years of hormonal therapy *(14-16)*. Absolute mortality reduction of about 2% has been shown for women with HR+ breast cancer who continue on tamoxifen for 10 years compared with those who stop after five years *(14)*. The recommendations in the American Society of Clinical Oncology clinical practice guideline on adjuvant endocrine therapy were updated on the basis of emerging data on the longer optimal duration of treatment, particularly adjuvant tamoxifen *(2)*. Aromatase inhibitors are not recommended for premenopausal women. For postmenopausal 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 *(17)*: aromatase inhibitors produced a 3.1% absolute decrease in recurrence compared with tamoxifen (5.0% versus 8.1%), and an absolute decrease in breast cancer mortality of 0.7% (1.7% versus 2.4%). Aromatase inhibitors should be advised only in patients at high risk of disease progression. When chemotherapy is administered, hormone therapy should always be initiated after the completion of chemotherapy.

Chemotherapy will add to benefit, particularly for women with large cancers and involved axillary lymph nodes *(3)*.

For patients with locally advanced cancer requiring preoperative (neoadjuvant) therapy, chemotherapy is usually the treatment of choice, although hormone therapy can sometimes be used in place of chemotherapy (in postmenopausal women).

Tamoxifen or an aromatase inhibitor plus ovarian suppression with a luteinizing hormone–releasing hormone (LHRH) agonist or oophorectomy can be considered for premenopausal patients at high risk of recurrence. The TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function Trial) trials compared the effect on disease-free survival of the aromatase inhibitor exemestane and of tamoxifen in premenopausal women also treated with ovarian suppression, and assessed the value of ovarian suppression in women receiving adjuvant tamoxifen. Primary analysis of these two phase III trials included data from 4690 patients. Disease-free survival for exemestane plus ovarian suppression and for tamoxifen plus ovarian suppression was 91.1% and 87.3%, respectively, after a median follow-up of 68 months *(18)*. The SOFT trial included 1084 women who remained premenopausal after completion of chemotherapy and were deemed to be at higher risk of recurrence. In this cohort, tamoxifen plus ovarian suppression compared with tamoxifen alone was associated with a 25% reduction in the relative risk of recurrence *(19)*.

HR-positive/HER2-positive tumours

As above, hormone therapy should be a component of the therapy for these patients. Chemotherapy plus trastuzumab should be administered to all patients except those with very small (<0.5 cm), node-negative tumours *(4)*. Combined hazard ratios (HR) for both overall survival and disease-free survival significantly support addition of trastuzumab (0.66 and 0.60, respectively). The risk of congestive heart failure and left ventricular ejection fraction decline was significantly increased by addition of trastuzumab (risk ratio 5.11 and 1.83 respectively), but the benefit far outweighed the risk for patients with high risk of recurrence and healthy heart *(20)*. The study with the longest follow-up concluded that, at 10 years, overall survival rate increased from 75.2% to 84.0% with the addition of trastuzumab to chemotherapy (HR 0.63) *(21)*. Trastuzumab should be administered for one year; typically, it is given concurrently with a taxane but not concurrently with an anthracycline. HER2-directed agents and hormone therapy can be given concurrently.

For patients receiving preoperative therapy, the combination of a taxane, trastuzumab and pertuzumab has been shown to be more effective than a taxane and trastuzumab alone *(22)*. However, the Expert Committee noted that further efficacy and safety data from clinical trials other than a single sponsor-driven trial are needed. The addition of pertuzumab as part of postoperative adjuvant therapy has not been shown to be beneficial. The role of trastuzumab–emtansine (T-DM1) as adjuvant therapy remains undefined; its effectiveness has been explored only in metastatic disease.

Neither pertuzumab nor trastuzumab–emtansine was proposed or recommended for inclusion in the EML at this time.

HR-negative/HER2-positive tumours

Hormone therapy is not indicated. Trastuzumab chemotherapy combinations are indicated.

HR-negative/HER2-negative tumours

Hormone therapies and trastuzumab-containing regimens are not indicated for these patients.

Standard chemotherapy regimens (non-trastuzumab regimens)

- **AC – doxorubicin and cyclophosphamide (every 3 weeks x 4 cycles), for subtypes 1 and 4 (and 2 and 3 if trastuzumab is unavailable)**
  - doxorubicin 60 mg/m^2 IV
  - cyclophosphamide 600 mg/m^2 IV

- **AC-T – doxorubicin/cyclophosphamide followed by paclitaxel or docetaxel for subtypes 1 and 4 (and 2 and 3 if trastuzumab is unavailable)**
  - doxorubicin 60 mg/m^2 IV every 3 weeks x 4 cycles
  - cyclophosphamide 600 mg/m^2 IV every 3 weeks x 4 cycles

  followed by
  - paclitaxel 175 mg/m^2 IV every 3 weeks x 4 cycles

  or
  - paclitaxel 80 mg/m^2 IV every 1 week x 12 weeks

  or
  - docetaxel 100 mg/m^2 IV every 3 weeks x 4 cycles

  Note: For paclitaxel the weekly schedule is superior to the 3-weekly schedule and should be used unless the patient is unable to come for weekly treatment.

- **TC – docetaxel/cyclophosphamide (every 3 weeks x 4 cycles) for subtypes 1 and 4 (and 2 and 3 if trastuzumab is unavailable)**
  - cyclophosphamide 600 mg/m^2 IV
  - docetaxel 75 mg/m^2 IV

- **Oral CMF (every 28 days for 6 cycles)**
  - cyclophosphamide 100 mg/m^2 orally, daily on days 1–14
  - methotrexate 40 mg/m^2 IV on days 1 and 8
  - 5-FU 600 mg/m^2 IV on days 1 and 8

Alternative regimen (if other regimens above are unavailable)

- **FAC (every 3 weeks x 6 cycles)**
  - 5-FU 500 mg/m^2 IV
  - doxorubicin 50 mg/m^2 IV
  - cyclophosphamide 500 mg/m^2 IV

Standard regimens including trastuzumab, for HER2-positive disease

- **AC-TH – doxorubicin/cyclophosphamide followed by paclitaxel/trastuzumab for subtypes 2 and 3**
  - doxorubicin 60 mg/m^2 IV every 3 weeks x 4 cycles
  - cyclophosphamide 600 mg/m^2 IV every 3 weeks x 4 cycles

  followed by
  - paclitaxel 80 mg/m^2 IV every 1 week x 12 weeks
  - trastuzumab[1] 2 mg/kg IV every 1 week x 12 weeks

  or
  - docetaxel 100 mg/m^2 IV every 3 weeks x 4 cycles
  - trastuzumab 2 mg/kg IV every 1 week x 12 weeks

  followed by
  - trastuzumab 6 mg/kg IV every 3 weeks to finish 1 year of therapy

- **TCH – docetaxel/carboplatin/trastuzumab for subtypes 2 and 3**
  - docetaxel 75 mg/m^2 IV every 3 weeks x 6 cycles
  - carboplatin AUC 6 IV every 3 weeks x 6 cycles
  - trastuzumab[2] 6 mg/kg IV every 3 weeks x 6 cycles

  followed by
  - trastuzumab 6 mg/kg IV every 3 weeks to complete 1 year of therapy

The application stated that epirubicin can be substituted for doxorubicin at an equipotent dose, and proposed that it be included in the EML as a class agent with doxorubicin for treatment of breast cancer. The Expert Committee considered that there was insufficient evidence to support the inclusion of epirubicin along with doxorubicin in the EML and did not recommend the inclusion of epirubicin as a within-class alternative to doxorubicin.

[1] Trastuzumab 4 mg/kg loading dose first week of therapy. (Alternatively, trastuzumab can be used with an 8-mg/kg bolus and maintenance of 6mg/kg every 3 weeks.)

[2] First dose of trastuzumab: loading dose 8 mg/kg.

Standard hormone regimens (pre- and postmenopausal women)

tamoxifen 20 mg/day orally x 5 years
LHRH agonist (goserelin) 3.6 mg/28 days SCI x 2–5 years[3]

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

anastrozole 1 mg/day orally x 5 years

The application proposed that anastrozole be added to the EML with a square box symbol as the pharmacological representative of the class of aromatase inhibitors and that this class should include letrozole and exemestane. The Expert Committee considered that this was reasonable.

With regard to hormone regimens, **premenopausal women** should receive tamoxifen for at least five years. Treatment for 10 years offers a small benefit compared with treatment for five years. For premenopausal women who have an absolute contraindication to, or are intolerant of, tamoxifen, ovarian suppression by surgery, radiation or medication in combination with an aromatase inhibitor is an acceptable alternative. Ovarian suppression plus tamoxifen or exemestane has been associated with improved disease-free survival and breast cancer-free survival in women at higher risk of recurrence.

Postmenopausal women can be treated with five years of an aromatase inhibitor, or two to three years of tamoxifen followed by an aromatase inhibitor to complete five years. Alternatively, five years' treatment with tamoxifen can be followed by five years of an aromatase inhibitor. Treatment for 10 years offers a small benefit compared with treatment for five years. If aromatase inhibitors are unavailable or if the patient is intolerant of an aromatase inhibitor, treatment with tamoxifen for the entire course is acceptable. Use of an aromatase inhibitor in the treatment course offers a small benefit for disease-free survival and marginal benefit for overall survival.

For postmenopausal women, five years of treatment with tamoxifen, followed by five years of treatment with an aromatase inhibitor, should be considered only in high-risk patients (e.g. node-positive).

Review of benefits and harms

Benefits

Hormone therapy reduces the risk of systemic recurrence by 50%, although the absolute benefit relates to the overall risk of relapse, which relates in turn to tumour size and grade and axillary nodal involvement. The improvement in relapse-free survival with chemotherapy varies by molecular subtype as well as overall risk of relapse, again based on

[3] Premenopausal patients at high risk of recurrence.

tumour size and grade and axillary nodal status. For patients with HER2-positive disease, the addition of trastuzumab to chemotherapy further reduces the risk of relapse significantly compared with chemotherapy alone. Moreover, the addition of trastuzumab to chemotherapy as preoperative 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 from taxanes. Paclitaxel and trastuzumab are associated with infusion reactions in up to 30–40% of patients; most reactions are mild and easily managed *(23, 24)*.

Tamoxifen can cause hot flushes, mood changes and, rarely, thromboembolic disease and endometrial cancer. Tamoxifen generally has a positive effect on bone density. Aromatase inhibitors can cause hot flushes, 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 *(12, 25, 26)*.

Bone marrow damage, myelodysplastic syndrome and acute leukaemia can occur after therapy with cyclophosphamide and doxorubicin but are rare.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended that the medicines in the following chemotherapy regimens, currently included on the complementary list of the EML, be specifically endorsed for the treatment of early-stage breast cancer. These regimens are suitable for use in HER2-positive and -negative disease, and in HR-positive and -negative disease.

Regimen	Medicines
AC	doxorubicin and cyclophosphamide
AC-T	doxorubicin and cyclophosphamide followed by paclitaxel
CMF	cyclophosphamide, methotrexate and 5-fluorouracil

The Committee also recommended that trastuzumab be added to the complementary list for treatment of HER2-positive early-stage breast cancer for use in AC-TH (doxorubicin and cyclophosphamide followed by trastuzumab and paclitaxel) and TC-H (docetaxel, carboplatin and trastuzumab) regimens. Where trastuzumab is unavailable, the

chemotherapy regimens listed above should be used (with or without hormone therapy as appropriate).

The Committee recommended that tamoxifen (already listed) be specifically endorsed for treatment of HR-positive early-stage breast cancer. In addition, the Committee recommended addition of anastrozole to the complementary list, with a square box symbol as the representative of the pharmacological class of aromatase inhibitors.

The Committee also considered that goserelin should be included on the complementary list for early-stage breast cancer. However, having earlier in the meeting recommended the listing of leuprorelin with a square box symbol as representative of the pharmacological class of LHRH agonists for treatment of metastatic prostate cancer, the Committee considered that a separate listing for goserelin was unnecessary as its availability would be captured by the square box listing for leuprorelin.

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