

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/m² IV
 - cyclophosphamide 600 mg/m² 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/m² IV every 3 weeks x 4 cycles
 - cyclophosphamide 600 mg/m² IV every 3 weeks x 4 cycles

followed by

 - paclitaxel 175 mg/m² IV every 3 weeks x 4 cycles

or

 - paclitaxel 80 mg/m² IV every 1 week x 12 weeks

or

 - docetaxel 100 mg/m² 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/m² IV
 - docetaxel 75 mg/m² IV
 - **Oral CMF (every 28 days for 6 cycles)**
 - cyclophosphamide 100 mg/m² orally, daily on days 1–14
 - methotrexate 40 mg/m² IV on days 1 and 8
 - 5-FU 600 mg/m² 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/m² IV
 - doxorubicin 50 mg/m² IV
 - cyclophosphamide 500 mg/m² 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/m² IV every 3 weeks x 4 cycles
 - cyclophosphamide 600 mg/m² IV every 3 weeks x 4 cycles
 - followed by*
 - paclitaxel 80 mg/m² IV every 1 week x 12 weeks
 - trastuzumab¹ 2 mg/kg IV every 1 week x 12 weeks
 - or
 - docetaxel 100 mg/m² 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/m² IV every 3 weeks x 6 cycles
 - carboplatin AUC 6 IV every 3 weeks x 6 cycles
 - trastuzumab² 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 years³

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 leuporelin 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 leuporelin.

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Metastatic breast cancer– EML

For the treatment of metastatic breast cancer, the application sought inclusion on the core list of the Model List of Essential Medicines of chemotherapy regimens utilizing cyclophosphamide, doxorubicin, paclitaxel or docetaxel, vinorelbine, capecitabine and gemcitabine administered as single agents, sequentially, for treatment of HER2-negative disease, trastuzumab (in combination with a taxane, vinorelbine or capecitabine) for patients with HER2-positive disease, and hormone therapies tamoxifen and anastrozole (as representative of the pharmacological class of aromatase inhibitors) for patients with hormone receptor-positive disease.

Cyclophosphamide, doxorubicin, paclitaxel, docetaxel and tamoxifen are currently included in the complementary list of the Model List. Vinorelbine, capecitabine, gemcitabine, trastuzumab and anastrozole were proposed for addition.

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

Introduction

Metastatic breast cancer is defined as disease beyond the breast and regional lymph nodes. Breast cancer can metastasize to any site in the body, including bones, liver, lung, serosal surfaces and brain. Although metastatic breast cancer is generally incurable, survival is highly variable: treatment is almost always indicated and patients can be treated and given palliative support with hormonal therapy, chemotherapy and/or targeted agents (1, 2).

Breast cancer is no longer viewed as a single disease but rather as a series of diseases defined by biological characteristics. Hormone receptor (HR) positive tumours demonstrate positivity for either estrogen receptors or progesterone receptors. Human epidermal growth factor receptor 2 (HER2) positive tumours overexpress the receptor HER2. Patients with HER2-positive disease typically have a worse prognosis.

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

1. HR-positive/HER2-negative
2. HR-positive/HER2-positive
3. HR-negative/HER2-positive
4. HR-negative/HER2-negative.

These biological subtypes help predict 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 patients with HER2-positive cancers.

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 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 (3). 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 (4). 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 (5). Women who receive treatment for early-stage breast cancer have a significantly higher chance of survival than those treated for metastatic disease. Even in less developed regions of the world, overall survival at 5 years for women treated for localized disease was 73.6% on average, compared with 47.4% for regional disease (4).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

The treatment of breast cancer should always be determined by pathological evaluation of the primary cancer. It is recommended that biopsy be performed by ultrasound-guided core needle technique, which will generally yield adequate tissue for histological and marker studies. 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. Surgical excision should be required only rarely, if needle biopsy is technically not feasible. Evaluation of the biopsy by an experienced pathologist will yield the histological subtype and grade of the cancer. Immunohistochemistry (IHC) analysis for estrogen receptors, and in some cases progesterone receptors, is critical since this will determine prognosis and whether the cancer is potentially sensitive to hormone therapy. HER2 can be assessed by either IHC or by fluorescence in situ hybridization if IHC is equivocal.

Testing

Staging should be performed to assess the extent of disease. Computerized tomography (CT) scans and bone scans can delineate the extent of metastatic disease. In more resource-constrained settings, a chest X-ray, liver ultrasound and plain films of bones that are painful are acceptable.

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. Intravenous fluids and antiemetics, as well as hypersensitivity medications, are required. Monitoring of complete blood count, 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 – especially if anthracycline doses remain below cumulatively toxic levels – and the potential benefit in disease control is substantial.

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 biological subtypes of breast cancer, followed by specific regimens.

HR-positive/HER2-negative tumours

Premenopausal patients should be treated initially with hormonal therapy, preferably tamoxifen, unless they were on tamoxifen at the time of the development of metastatic disease. Patients who are tolerating tamoxifen should be treated until there are clear signs of tumour progression. Stable disease is an indication to continue tamoxifen therapy. Aromatase inhibitors are not recommended for premenopausal women who should undergo either oophorectomy or ovarian suppression with a luteinizing hormone-releasing hormone agonist.

Women who are postmenopausal (naturally, surgically or chemically) can be treated with tamoxifen or an aromatase inhibitor. If they were on tamoxifen at the time of development of metastatic disease, they should be treated with an aromatase inhibitor. Treatment should continue until there is clear evidence of tumour progression, at which time the patient should be converted to the other agent (from tamoxifen to an aromatase inhibitor or vice versa). Stable disease is an indication to continue hormone therapy.

At the time of tumour progression, sequential single-agent chemotherapy should be used, unless there is rapidly progressive disease or high disease burden that requires a rapid

response, in which case combination chemotherapy can be used (1). Patients who were treated in the adjuvant setting with chemotherapy 12 months or less from the time of developing metastatic disease should be treated with chemotherapy agents other than those received in the adjuvant setting.

HR-positive/HER2-positive tumours

As above, hormone therapy should always be a component of the therapy for these patients; the factors that determine choice of therapy are the same as for patients with HR-positive/HER2-negative tumours.

Chemotherapy and trastuzumab should be initiated concurrently with hormone therapy. Typically trastuzumab is given concurrently with a taxane and not given concurrently with an anthracycline; however, trastuzumab can be given concurrently with other cytotoxic agents, such as vinorelbine.

HR-negative/HER2-positive tumours

Hormone therapy is not indicated. Trastuzumab chemotherapy combinations as described above for patients with HR-positive/HER2-positive tumours are indicated.

HR-negative/HER2-negative tumours

Hormone therapies and trastuzumab-containing regimens are not indicated for these patients. Sequential single-agent chemotherapy should be used, unless there is need for rapid control of disease due to visceral crisis or very high tumour burden (1, 6). The application stated that choice among recommended chemotherapeutic agents is arbitrary – there are no data to suggest that initial treatment with one agent is more efficacious than another. The only exception is that patients who were treated in the adjuvant setting with chemotherapy 12 months or less from the time of developing metastatic disease should be treated with agents other than those received in the adjuvant setting.

Standard chemotherapy regimens (non-trastuzumab regimens)

- **Doxorubicin, for subtypes 1 and 4 (and 2 and 3 if trastuzumab is unavailable)**
 - doxorubicin 60 mg/m² IV every 3 weeks

Note: Cumulative dose of doxorubicin should not exceed 450 mg/m² because of the increased likelihood of severe cardiomyopathy with increasing dose.
- **Paclitaxel, for subtypes 1 and 4 (and 2 and 3 if trastuzumab is unavailable)**
 - paclitaxel 175 mg/m² IV every 3 weeks⁴
 - or
 - paclitaxel 80 mg/m² IV weekly

⁴ Weekly paclitaxel is the more efficacious option but requires more frequent visits.

Standard regimens including trastuzumab, for HER2-positive disease

- **Paclitaxel and trastuzumab, for subtypes 2 and 3**
 - paclitaxel 80 mg/m² IV weekly
 - trastuzumab 2 mg/kg IV weekly (following loading dose of 4mg/kg)
- **Docetaxel and trastuzumab, for subtypes 2 and 3**
 - docetaxel 60–75 mg/m² IV every 3 weeks
 - trastuzumab 6 mg/kg IV every 3 weeks (following loading dose of 8mg/kg)

Single-agent chemotherapy regimens, for HER2-negative disease

The application stated that capecitabine, vinorelbine and gemcitabine have all been shown to have activity for patients with metastatic breast cancer, and can be supported to be given as single agents for patients with HER2-negative breast cancer. For patients with HER2-positive breast cancer trastuzumab has also been given with vinorelbine, successfully. These regimens are listed below.

- **Capecitabine (single agent)**
 - capecitabine 2000 mg/m² per day orally in two divided doses on days 1–14 of 21-day cycle
- **Vinorelbine (single agent)**
 - vinorelbine 25 mg/m² IV weekly
- **Gemcitabine (single agent)**
 - gemcitabine 1000 mg/m² IV on days 1 and 8 of 21-day cycle
- **Cyclophosphamide (single agent)**
 - cyclophosphamide 1000 mg/m² IV on day 1 of a 21-day cycle

Capecitabine is an alternative to paclitaxel in patients for whom anthracycline treatment has failed and for elderly patients or women wishing to avoid the adverse effects associated with cyclophosphamide, methotrexate and fluorouracil (7). Compared indirectly with vinorelbine, capecitabine was associated with lower costs and improved patient outcomes (8). Vinorelbine has a similar efficacy and toxicity profile to standard first-line chemotherapy with anthracyclines and other non-taxane-containing regimens (9).

Single-agent chemotherapy regimens, for HER2-positive disease

- **Vinorelbine (with trastuzumab)**
 - vinorelbine 25 mg/m² IV weekly
with either
 - trastuzumab 2 mg/kg IV weekly (following loading dose of 4mg/kg)
 - or
 - trastuzumab 6 mg/kg IV every 3 weeks (following loading dose of 8mg/kg)

Standard hormone regimens

- tamoxifen 20 mg/day orally until tumour progression
- or
- anastrozole 1 mg/day orally until tumour progression

Aromatase inhibitors should be used only in postmenopausal women (natural or surgical) or premenopausal women who are receiving ovarian suppression.

Premenopausal women should receive tamoxifen, in addition to ovarian ablation (surgical) or ovarian suppression, until tumour progression. Postmenopausal women can be treated with either tamoxifen or an aromatase inhibitor, but not both concurrently. If there is tumour progression during treatment with one of these agents, that agent should be stopped and the other initiated. Sequential use of these agents results in increased survival and improved quality of life: delay in time to tumour progression results in increased time until use of chemotherapy becomes necessary (10).

Review of benefits and harms

Benefits

Hormone therapy will yield clinical benefit for approximately half of the patients who have tumours that are estrogen- and/or progesterone-receptor-positive. Clinical benefit is defined by either reduction in tumour size or disease stability for at least several months. Patients who experience clinical benefit generally have a reduction in symptoms, improved quality of life and prolonged survival.

For about one third of patients who have had progressive disease on hormone therapy or have estrogen- and/or progesterone-receptor-negative disease, chemotherapy can lead to a reduction in tumour burden. Patients who benefit from chemotherapy have a reduction in symptoms, improved quality of life and a modest prolongation of survival.

A 2013 Cochrane systematic review of 12 trials comparing combination with sequential single-agent chemotherapy for metastatic breast cancer found there to be no difference in overall survival between the two groups (hazard ratio (HR) 1.04; 95% CI: 0.93–1.16; $P = 0.45$). The review also found some evidence of a higher risk of progression in the combination arm (HR 1.11; 95% CI: 0.99–1.25; $P = 0.08$). Overall tumour response rates were higher in the combination arm (RR 1.16; 95% CI: 1.06–1.28; $P = 0.001$), as was the risk of febrile neutropenia (risk ratio (RR) 1.32; 95% CI: 1.06–1.65; $P = 0.01$). The authors concluded that the findings supported recommendations in international guidelines for the use of sequential monotherapy unless there is rapid disease progression (6).

The Expert Committee considered that the evidence showed that gemcitabine is not a highly effective treatment for metastatic breast cancer. A meta-analysis of nine randomized controlled trials (2651 patients) revealed that, compared with gemcitabine-free chemotherapy, gemcitabine-based therapy offered no improvement in terms of time to

progression (HR 0.91; 95% CI: 0.72–1.15; $P = 0.44$) or overall survival (HR 1.05; 95% CI: 0.88–1.25; $P = 0.60$) (11). The rates of grade 3 and 4 anaemia (HR 2.02; 95% CI: 1.35–3.02; $P = 0.006$), neutropenia (HR 2.33; 95% CI: 1.37–3.63; $P = 0.01$) and thrombocytopenia (HR 8.31; 95% CI: 5.00–13.82; $P < 0.0001$) were significantly higher in the gemcitabine-based arm. The authors concluded that gemcitabine-based chemotherapy was as effective as gemcitabine-free chemotherapy in patients with metastatic breast cancer but with increased haematological toxicity.

For patients with HER2-positive disease, the addition of trastuzumab to chemotherapy dramatically increases the response rate and overall survival. Typically, trastuzumab is given concurrently with a taxane, but patients may be treated with trastuzumab and vinorelbine or capecitabine (1).

A Cochrane systematic review of seven randomized controlled trials comparing trastuzumab alone or in combination with chemotherapy, hormonal therapy or targeted agents against the same regimen without trastuzumab (control) in 1497 women with HER2-positive metastatic breast cancer reported that adjuvant trastuzumab as first-line treatment improves survival but may increase the risk of heart failure (12). Trastuzumab-containing regimens were favoured for overall survival and progression-free survival (HR 0.82; 95% CI: 0.71–0.94, $P = 0.004$; and HR 0.61; 95% CI: 0.54–0.70, $P < 0.00001$, respectively; moderate-quality evidence). Trastuzumab was associated with increasing rates of heart failure (RR 3.49; 90% CI: 1.88–6.47, $P = 0.0009$; moderate-quality evidence) and left ventricular ejection fraction decline (RR 2.65; 90% CI: 1.48–4.74; $P = 0.006$). The authors concluded that studies that administered trastuzumab as first-line treatment, or along with a taxane-based regimen, improved mortality outcomes. The evidence to support the use of trastuzumab beyond progression is limited.

The Committee noted that, since submission of the application, final results of the CLEOPATRA study have been published (13). This study compared the efficacy and safety of pertuzumab, trastuzumab and docetaxel versus placebo, trastuzumab and docetaxel as first-line treatments in patients with HER2-positive metastatic breast cancer. Deaths were reported in 168/402 patients (41.8%) in the pertuzumab group and in 221/406 patients (54.4%) patients in the control group (HR favouring the pertuzumab group, 0.68; 95% CI: 0.56–0.84; $P < 0.001$). The difference in median overall survival between the two groups was 15.7 months: 56.5 months (95% CI: 49.3 to not reached) in the pertuzumab group and 40.8 months (95% CI: 35.8–48.3) in the placebo group (HR favouring the pertuzumab group 0.68; 95% CI: 0.56–0.84; $P < 0.001$). The Expert Committee considered that the CLEOPATRA results are notable for their clinical relevance, but further efficacy and safety data from clinical trials other than single sponsor-driven trials are needed. In particular, the Committee considered that additional evidence is needed in women previously exposed to trastuzumab in the adjuvant setting. Pertuzumab was neither proposed nor recommended for inclusion in the EML at this time.

Harms and toxicity considerations

Common

Risks of treatment include common short-term toxicities such as alopecia, neutropenia, fever and infection, and neuropathy (affecting 15–60% of patients) from taxanes. Paclitaxel and trastuzumab are both associated with infusion reactions in up to 30–40% of patients; most infusion reactions are mild and easily managed (14, 15).

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

Vinorelbine often causes severe neutropenia and granulocytopenia, which increase patients' risk of infection. Like other vinca alkaloids, vinorelbine also frequently causes constipation. It is a strong vesicant, and care must be taken to avoid extravasation and associated tissue damage (16).

Palmar–plantar erythrodysesthesia (hand–foot syndrome) is associated with capecitabine, with an increased incidence of up to 60% in patients treated with capecitabine. This adverse effect typically resolves following interruption of treatment (17).

Gemcitabine frequently causes myelosuppression with dose-limiting thrombocytopenia and leukopenia with associated risk of infection. Gemcitabine is also associated with increased hepatic transaminases, which may lead to more severe hepatotoxicity in up to 10% of patients. Many patients experience oedema and dyspnoea (18).

Serious

Cardiac muscle suppression or cardiac 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 (19–21). Rare incidences of bone marrow damage, myelodysplastic syndrome and acute leukaemia can occur after therapy with doxorubicin. Diarrhoea occurs in up to 50% of patients treated with capecitabine. Diarrhoea can be severe, may require hospital admission for intravenous fluid replacement and is often dose-limiting (22).

Recommendations

On the basis of the evidence presented in the application, the Committee made the following recommendations in relation to treatments for metastatic breast cancer:

- Trastuzumab should be added to the complementary list of the EML for the treatment of HER2-positive metastatic breast cancer.
- Capecitabine and intravenous vinorelbine should be added to the complementary list of the EML for the treatment of metastatic breast cancer. The Committee noted that orally administered vinorelbine is better tolerated but is more costly, so

recommended inclusion only of the intravenous formulation of vinorelbine at this time.

- Doxorubicin, paclitaxel, docetaxel and cyclophosphamide, currently on the complementary list, should be endorsed for use in the treatment of metastatic breast cancer.
- Tamoxifen should be specifically endorsed for treatment of HR-positive metastatic breast cancer.
- Anastrozole should be added to the complementary Model List for treatment of HR-positive metastatic breast cancer, with a square box symbol as representative of the therapeutic class of aromatase inhibitors.
- Inclusion of gemcitabine on the Model List is not recommended at this time, as the available evidence did not support an advantage of gemcitabine-based therapy over gemcitabine-free therapy in terms of time to progression and overall survival.

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