THE MANAGEMENT OF BREAST CANCER

This document is a practical decision guide reflecting current policies of the SW Wales Cancer Network Breast Group.

Recommendations are based on the most recent versions of guidelines from NICE, SIGN, BASO, RCR, NCCN, ASCO, EORTC, St Gallen and ESMO, modified and integrated when appropriate to reflect local consensus on optimal care of breast cancer.

Participation in clinical trials should always be considered a priority. 'Clinical trial boxes' in the following pages remind of the main eligibility criteria and design of currently open trials. Please refer to the South West Wales Clinical Trial Portfolio to know what is the nearest centre in the Network where a trial of interest is open, and for contact details.

VERSION 5 – February 2011

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MAIN CHANGES in this update:

Adjuvant systemic therapy
New recommendations for the choice of chemotherapy regimens

Prophylactic G-CSF
New recommendations based on 2010 EORTC guidelines

1. EARLY INVASIVE BREAST CANCER: STAGING

1.1 Pre-surgical staging

In all patients:
- bilateral mammography
- FBC and biochemistry including LFTs and calcium.

Bone scan in case of:
- abnormal alkaline phosphatase
- symptoms

CT neck-thorax-abdomen in case of:
- clinical tumour size >5 cm
- clinical T4
- palpable nodes or nodes proved positive on FNA/core biopsy.

Contrast enhanced breast MRI in
- all patients with an occult primary (see section 11.6)
- selected patients where multifocality is suspected, or cannot be excluded e.g. patients with severe generalised benign change on ultrasound
- selected patients where there is significant discrepancy between clinical and ultrasound tumour size measurement
- patients with lobular cancer, especially if they have chosen breast conservation or have mammograms difficult to interpret because of breast density.

1.2 Post-surgical staging

CT neck-thorax-abdomen and bone scan (if not done pre-surgery) if:
- pathological tumour size >5 cm
- pT4
- node positive.

1.3 Pathology data set

The following histopathology data are important for treatment decisions and must be available at the time of the MDT discussion of new patients:
- Pathological tumour size
- Grade
- Type
- ER and PgR status (Allred score)
- HER2 status (IHC, confirmed by FISH if score 2+)
- Lymphatic/vascular invasion
- Margins
- Presence of in situ disease
- Number of involved nodes and total number of nodes identified

- Characteristics of positive nodes (micro- or macrometastasis; technique used (H&E, IHC); presence or absence of extracapsular involvement)
- TNM classification (7^{th} edition).

Because of the timing for HER2 status assessment (especially when FISH confirmation is needed), any MDT treatment recommendation made in the absence of HER2 results needs to be reviewed by the responsible clinician when the HER2 status becomes available. If appropriate, the case will be brought back to the MDT for re-discussion.

2. BREAST CANCER IN SITU

2.1 Lobular carcinoma in situ

LCIS is often an incidental finding, and although its presence is a risk factor for recurrence, this can occur anywhere in either breast. Therefore identification of LCIS does not impact upon treatment decisions. An exception is pleomorphic lobular carcinoma in situ for which mastectomy may be considered.

2.2 Ductal carcinoma in situ

Surgery. Women with DCIS are usually treated with breast conserving surgery. Margins of less than 2 mm are an indication for re-excision. Mastectomy may be required in case of multifocal or diffuse DCIS.
Axillary staging is not usually required but sampling may be considered during mastectomy when the risk of finding invasive disease at surgery is greater (high grade, extensive, or palpable DCIS).

Radiotherapy. Radiotherapy to the breast (4000 cGy in 15 fractions) is normally recommended for DCIS treated with conservative surgery, but may be omitted in low grade DCIS excised with wide margins.

Endocrine therapy. Postmenopausal patients with ER+ DCIS treated with conservative surgery should be considered for the IBIS-II DCIS trial. Outside the trial, selected women may be offered tamoxifen (after a discussion of risks and benefits) to reduce the risk of recurrence, although there is no evidence of a reduction in mortality.

IBIS-II DCIS

Main eligibility criteria: postmenopausal, age 40-70, conservative surgery for ER+ DCIS with margins $\geq$1 mm.

Randomisation: tamoxifen vs. anastrozole (5 yrs).

3. EARLY INVASIVE BREAST CANCER: SURGERY

3.1 Conservative surgery

Women with early stage invasive breast cancer are offered breast-conserving surgery (wide local excision) followed by radiotherapy, as an alternative to mastectomy, whenever this is appropriate. Surgical clips should be routinely placed in the tumour bed to help radiotherapy planning.
Contraindications to conservative surgery are:

- multifocal disease
- unfavourable ratio of tumour size to breast size
- unable or unwilling to attend follow up
- unable or unwilling to receive radiotherapy
- unsuitable for radiotherapy (e.g. previous radiotherapy to the same breast, connective tissue disease)

If radial margins are less than 1 mm, re-excise tumour margins. If still less than 1 mm, particularly if extensive ductal carcinoma in situ present (> 25% of tumour bearing area), consider mastectomy.
Posterior tumour margin abutting on pectoral fascia is acceptable even if tumour margin <1mm.
Anterior margin < 1mm is acceptable if the excision extends up to the sub-cutaneous fascia.
Breast reconstruction (immediate or deferred) should be considered for suitable patients treated by mastectomy.

3.2 Axillary staging

All invasive tumours must have axillary staging.
Axillary clearance is the standard staging procedure for patients with clinically or radiologically positive nodes.
Sentinel node biopsy is offered to patients with no preoperative evidence of nodal involvement. Clearance of the axilla is however indicated if nodal metastases are found in sampled nodes or in the sentinel node(s), including micrometastases (pN1mi, greater than 0.2 mm but not greater than 2.0 mm).

4. ADJUVANT RADIOTHERAPY

4.1 Radiotherapy after conservative surgery

Radiotherapy to the breast (4000 cGy in 15 fractions) is indicated in all patients treated with conservative surgery for invasive breast cancer.
A boost of 1600 cGy in 8 fractions is indicated for all patients aged <40 and for those with margins <2 mm. In patients aged 40-50, relative indications for a boost are Grade 3 or lymphovascular invasion.

4.2 Post-mastectomy radiotherapy

Radiotherapy to the chest wall (4000 cGy in 15 fractions) is indicated as a standard treatment in the following cases:

- 4 or more positive nodes (SCF field is included in these patients)
- extension to chest wall or skin

- inflammatory carcinomas.

Patients with relative indications for post mastectomy radiotherapy should be discussed with a Clinical Oncologist and considered for participation in the SUPREMO trial. Relative indications include tumour size ≥50 mm, 1-3 positive nodes, grade 3, significant LVI, close margins.

SUPREMO

Main eligibility criteria:
- 1-3 nodes positive
- node negative with risk factors:
    - T2 if grade 3 and/or LVI+
    - multifocal if grade 3 and/or LVI+

Randomisation: chest wall RT vs. control.

4.3 Radiotherapy to the axilla

Node-negative patients and node-positive patients who have undergone axillary clearance do not need axillary radiotherapy, unless there is a macroscopic axillary residual following clearance. Node-positive patients who have undergone axillary sampling should be considered for axillary radiotherapy if axillary clearance (the recommended option) is not carried out.

5. ADJUVANT SYSTEMIC THERAPY: INDICATIONS

According to the 2009 St Gallen Consensus Conference, systemic adjuvant therapy decisions are clear-cut in the following groups of patients:

- adjuvant endocrine therapy (see section 7) is indicated in patients with endocrine responsive tumours (defined as having tumours with any expression of oestrogen receptors)
- adjuvant anti-HER2 therapy (see section 8) is indicated in patients with HER2 positive tumours
- adjuvant chemotherapy (see section 6) is indicated in patients with triple-negative tumours and, with anti-HER2 therapy, in patients with HER2 positive tumours.

The remaining patients – those with ER-positive, HER2-negative disease - are the group in whom decisions about adjuvant chemotherapy are most difficult.

Relative indications for chemotherapy (in addition to endocrine therapy) in patients with ER-positive, HER2-negative disease are:
- lower ER and PgR level
- grade 3
- high proliferation index (e.g. Ki67)
- four or more positive nodes
- extensive lymphovascular invasion
- tumour size >5 cm
- high recurrence score in multigene assays
- patient preference to use all available treatments.

Relative indications for endocrine therapy alone (avoiding chemotherapy) in patients with ER-positive, HER2-negative disease are:

- higher ER and PgR level
- grade 1
- low proliferation index (e.g. Ki67)
- negative nodes
- absence of extensive lymphovascular invasion
- tumour size $\leq$2 cm
- low recurrence score in multigene assays
- patient preference to avoid chemotherapy-related side effects.
-

Factors that individually provide little guidance in reaching a decision on chemotherapy in patients with ER-positive, HER2-negative disease include:

- grade 2
- intermediate proliferation or recurrence scores
- presence of one to three positive lymphnodes
- tumour size between 2.1 and 5 cm.

However, if all these intermediate factors are present, this usually tips the balance towards the use of chemotherapy.

Some patients with triple-negative, node-negative tumours of rare histological type (medullary, apocrine and adenoid cystic breast cancers) or with very small primary tumours (pT1a) might be spared adjuvant systemic therapy if there are no other signs of increased metastatic potential.

Gene-profiling tests are not yet available in the NHS but eligible patients should be considered for the Oncotype DX study.

SOUTH WALES ONCOTYPE DX STUDY

Main eligibility criteria: ER+, node negative (or N1itc, N1mic) patients with early breast cancer, potentially fit for adjuvant chemotherapy in addition to hormone therapy

Study design: comparison of treatment decisions before and after multigene assay with Oncotype DX

Patients should also be screened for eligibility into the REACT trial.

REACT

Main eligibility criteria:

- postmenopausal ER+ HER2-ve patients (with or without chemotherapy), node positive or node-negative at intermediate-high risk of recurrence (T>2 cm, or LVI, or grade 2-3)
- pre- or postmenopausal triple negative patients after adjuvant chemotherapy

Randomisation: celecoxib 400 mg od for 2 years vs. placebo

6. ADJUVANT CHEMOTHERAPY

Patients with indications for chemotherapy should discuss this option with an oncologist. Adjuvant! (www.adjuvantonline.com) is a helpful tool to assist discussion of treatment options with patients. Adjuvant! however does not take into account HER2 status or lymphovascular invasion, and is not suitable for patients with multicentric tumours, bilateral cancers, or those who have received neoadjuvant treatment. A new version of Adjuvant! (www.newadjuvant.com) which takes into account HER2 status is also available although not yet officially released for clinical use.

6.1 Chemotherapy regimens

The following standard adjuvant regimens are available for prescription through the Network's electronic system (Chemocare):

$FE_{100}C$. Fluorouracil 500 mg/ m2, Epirubicin 100 mg/m2, Cyclophosphamide 500 mg/m2 day 1 every 21 days x 6

Epi-CMF. Epirubicin 100 mg/m2 every 21 days x 4, followed by cyclophosphamide 600 mg/m2, methotrexate 40 mg/2, fluorouracil 600 mg/m2 day 1 and 8 every 28 days x 4.

TAC. Docetaxel 75 mg/m2, doxorubicin 50 mg/m2, cyclophosphamide 500 mg/m2 day 1 every 21 days x 6

FEC→D. Fluorouracil 500 mg/m2, epirubicin 100 mg/m2, cyclophosphamide 500 mg m/2 day 1 every 21 days x 3, followed by docetaxel 100 mg/m2 every 21 days x 3

AC→D. Doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 day 1 every 21 days x 4, followed by docetaxel 100 mg/m2 every 21 days x 4

TCbH. Carboplatin AUC 6 and docetaxel 75 mg/m2 day 1 every 21 days x 6, plus trastuzumab (starting with cycle 1, and continued after chemotherapy to complete 1 year)

TC. Docetaxel 75 mg/m2 and cyclophosphamide 600 mg/m2, day 1 every 21 days x 4

Dose-dense AC→P. Doxorubicin 60 mg/m2, and cyclophosphamide 600 mg/m2 day 1 every 14 days x 4, followed by paclitaxel 175 mg/m2 day 1 every 14 days x 4, all with GCSF support.

The current consensus among the Network's oncologists is:
- TCx4 is adequate in the majority of node-negative, ER positive patients and in elderly patients (biologic age>70)
- Node positive patients should be offered TAC or FEC-D
- Patients at very high risk of recurrence (triple negative or heavily node positive) may be good candidates for dose-dense chemotherapy
- HER2 positive patients are preferentially treated with the TCbH regimen.

All regimens associated with >20% risk of febrile neutropenia (i.e., all taxane-containing regimens) should be given with primary prophylactic GCSF (see Section 14).
The dose of chemotherapy must be calculated based on actual body weight. Dose capping may result in under treatment of obese patients.

6.2 Cardiac safety of anthracyclines

Anthracyclines are generally contraindicated in case of:
- history of documented congestive heart failure or MI
- angina requiring medication
- uncontrolled hypertension
- unstable arrhythmias
- clinically significant valvular disease
- prior treatment with anthracyclines, and cumulative dose (including the new treatment) above 450 mg/m2 for doxorubicin or 900 mg/m2 for epirubicin.

A baseline LVEF assessment (with MUGA scan or echocardiogram) should be obtained prior to anthracyclines in patients with risk factors such as long-standing hypertension or age >65.

In patients with contraindications to anthracycline-containing regimens, anthracycline-free regimens such as TC or TCH should be considered.

6.3 Chemotherapy in elderly patients

The benefits of adjuvant chemotherapy are uncertain in patients over 70 because of the small number of patients from this age group included in trials. However, biologic age rather than chronologic age should be used for treatment decisions on a case-by-case basis.

7. ADJUVANT HORMONE THERAPY

7. 1 Definition of menopause

It is necessary to clearly establish menopausal status prior to discussion of the appropriate hormonal therapy for a patient.
Many patients will have a treatment-induced amenorrhoea either from chemotherapy or prior tamoxifen. Treatment induced amenorrhoea cannot be considered a reliable indication of menopause and interpretation of gonadotropin and oestradiol measurements can be difficult and must be used with caution.
If in doubt that a woman is postmenopausal, tamoxifen should be used.

A woman will be considered postmenopausal in case of

- Hysterectomy and age > 55, or
- Natural amenorrhoea (not chemo-induced) for >12 months, or
- Bilateral oophorectomy.

7. 2 Adjuvant endocrine therapy

All women with oestrogen receptor positive (ER+ve; Allred score >=3) tumours should be offered adjuvant endocrine treatment. Although the significance of PgR positivity in ER negative breast cancer is uncertain, ER-PgR+ patients should also be offered endocrine treatment.
Adjuvant hormonal therapy produces significantly better outcomes in women with ER+ve tumours. There is no evidence of benefit to patients whose tumours are oestrogen and progesterone receptor negative.
Oestrogen receptor (ER) status should be measured for all women prior to discussion of adjuvant therapy, and is considered positive where the Allred score is 3 or above.
The type of endocrine therapy selected is based on the menopausal status of the patient.

7. 3 Premenopausal women

Pre-menopausal women should have tamoxifen at a dose of 20 mg a day for at least 5 years. This remains the gold standard for pre-menopausal women.
Concomitant treatment with inhibitors of cytocrome P450, such as certain selective serotonine reuptake inhibitors (paroxetine, fluoxetine) may reduce the efficacy of tamoxifen, by decreasing plasma levels of the active metabolite endoxifen. Patients on tamoxifen should avoid paroxetine and fluoxetine, and consider switching to other SSRIs (venlafaxine and citalopram) having only minimal effect on tamoxifen metabolism.
There is some new evidence to support the continued use of tamoxifen after five years; however prolonged use of tamoxifen does increase the risk of endometrial cancer. If the patient has become postmenopausal, switching to letrozole is a preferred strategy if extended adjuvant endocrine treatment is being considered.
Premenopausal patients who have severe intolerance of tamoxifen may also be considered for a switch to aromatase inhibitors, with concomitant ovarian suppression.

7. 4 Postmenopausal women

Initial treatment. An aromatase inhibitor (AI) should be given as their initial adjuvant therapy to all post-menopausal patients with hormone-sensitive early breast cancer. Whilst the absolute benefit of endocrine therapy is small to women in the very good prognostic group (i.e. T1 G1 N0 HER2 negative), aromatase inhibitors also reduce the risk of new contra-lateral primary tumours compared with tamoxifen. In light of this it is recommended that all postmenopausal women with endocrine sensitive breast cancer should be offered a licensed aromatase inhibitor (anastrozole or letrozole); the agent of choice is letrozole in view of recent results of randomized trials suggesting an overall survival benefit with letrozole compared to tamoxifen.
Aromatase inhibitors after tamoxifen. If an aromatase inhibitor has not been prescribed as first line adjuvant therapy, switching to a licensed aromatase inhibitor (exemestane or anastrozole) after 2-3 years of tamoxifen is recommended. If the patient has been on tamoxifen for 4.5-6 years (for instance women who were premenopausal at the time of diagnosis, but have become postmenopausal by the time they complete tamoxifen), then the recommended treatment is letrozole as extended adjuvant therapy. A treatment-free gap after cessation of tamoxifen is not a contraindication to extended adjuvant therapy with letrozole.

Duration of therapy. No clear guidance can be given on the optimum duration of treatment from the current available data. Benefits in reducing relapse have been seen in the extended adjuvant trials. Therefore by inference there may be benefits in extending therapy beyond 5 years particularly

in node positive and other high risk patient groups. Discussion to extend therapy beyond five years should be done on an individual patient basis.

Side effects. When prescribing aromatase inhibitors, a discussion should take place with the patient regarding absolute benefit balanced against potential side effects. Side effects reported with AIs include increase in the number of fractures due to osteoporosis, arthralgia and myalgia. There are however fewer incidences of gynaecological side effects and thromboembolic events than with tamoxifen. Aromatase inhibitors should not be used alone for pre-menopausal women.
Patients who do not tolerate an aromatase inhibitor may occasionally benefit from switching to another aromatase inhibitor. Switching to tamoxifen can also be considered.

7.5 Primary endocrine therapy

Outside trials (see section 9 for POETIC trial) primary endocrine therapy is not a substitute for the established methods of surgery and radiotherapy, and should only be used first-line if the patient is very infirm or refuses surgery. Surgery with or without radiotherapy remains the treatment of choice for the majority of elderly patients.

The main indications for primary endocrine therapy are:
- Selected postmenopausal ER+ve patients with operable breast cancer >4 cm size who express a strong desire to avoid mastectomy, and in whom primary chemotherapy is considered unsuitable.
- Patients with any tumour who are truly unfit for surgery or primary chemotherapy.
- Patients who refuse surgery and in whom primary chemotherapy is considered unsuitable.
- Patients with T4 breast cancer and in whom primary chemotherapy is considered unsuitable.
- As part of a clinical trial.

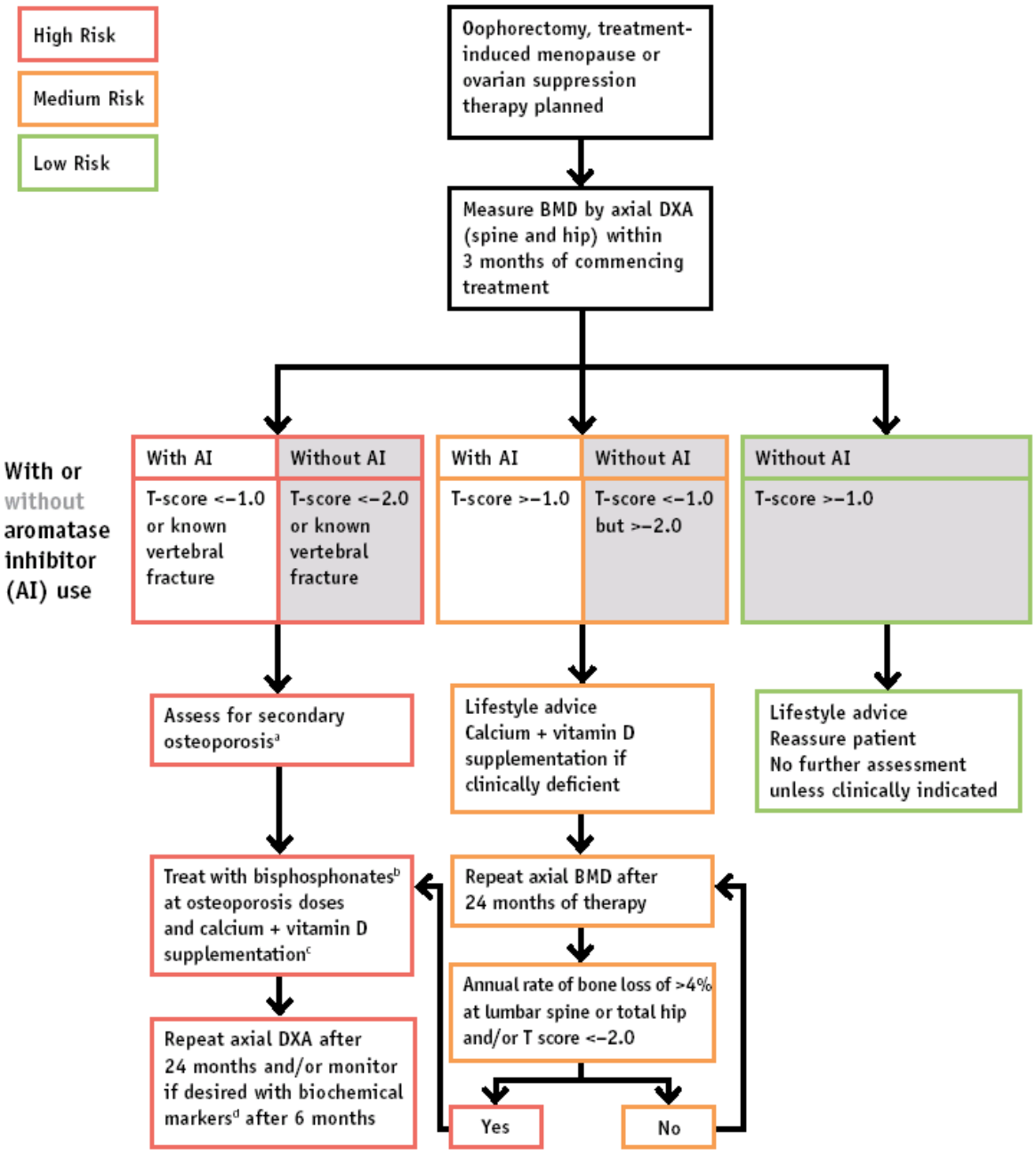
It is recommended that aromatase inhibitors are used in the first instance as these have proven to be more effective than tamoxifen. Letrozole is the only licensed aromatase inhibitor in this setting. Letrozole 2.5 mg/day should be used as first line therapy for these groups of patients.

Delay of surgery for personal reasons. Primary endocrine therapy should not be given routinely prior to surgical treatment. Tamoxifen increases thromboembolic risk, and interferes with the mechanism of action of chemotherapy. However there are occasions when surgical treatment is delayed due to patients' circumstances. If this is to be beyond 2 months, primary endocrine therapy is appropriate if the patient is ER+ve.

7.6 Bone health

Guidance on the evaluation, monitoring and treatment of bone loss in early breast cancer is provided by the NCRI Breast Group and National Osteoporosis Society. Two algorithms (for patients who experience premature menopause and for postmenopausal patients on AIs) are provided.

Algorithm 1: Adjuvant treatment associated with ovarian suppression/failure with or without concomitant aromatase inhibitor use in women who experience premature menopause



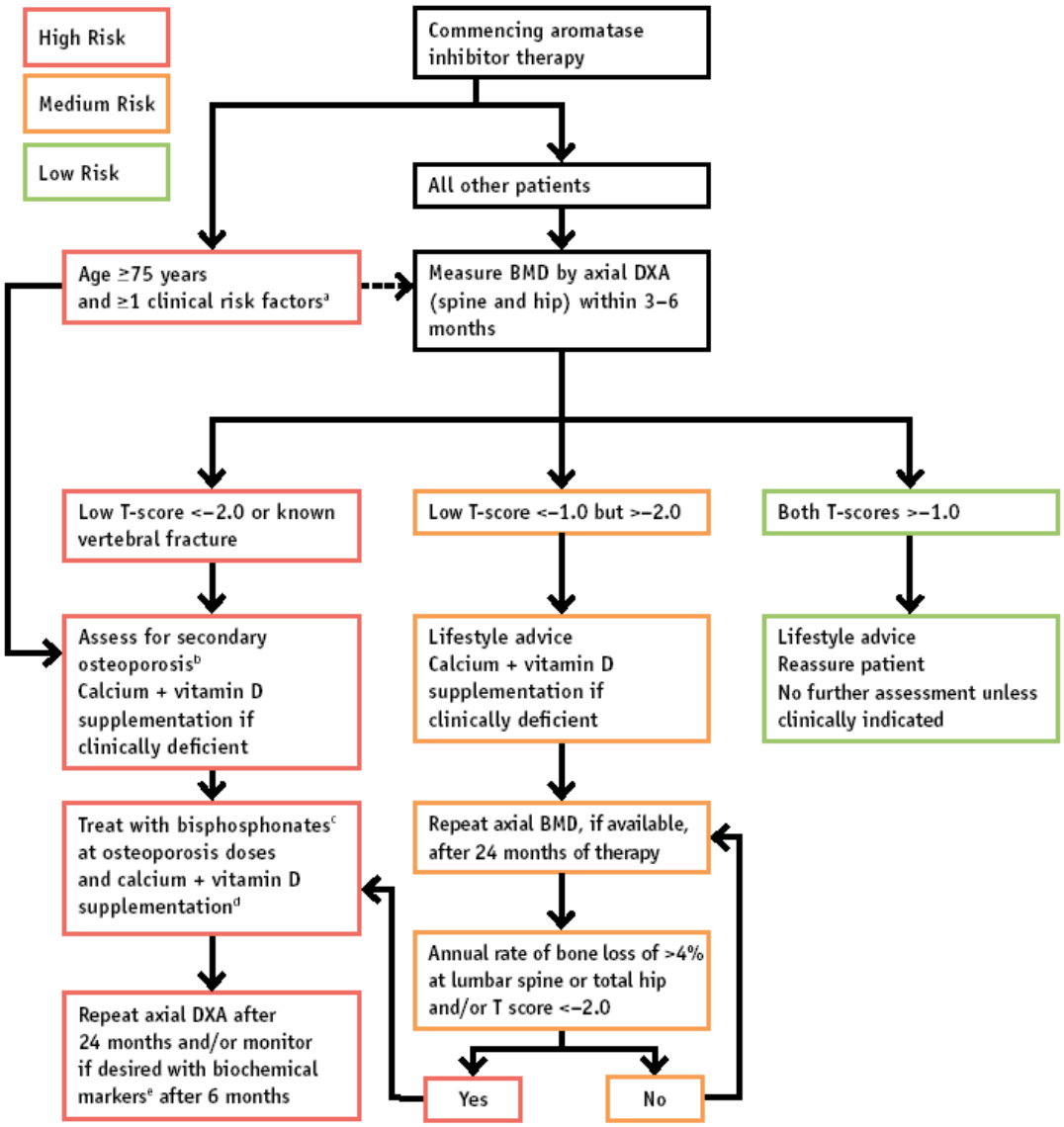
a ESR, FBC, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST / ±GT), serum creatinine, endomysial antibodies, serum thyroid-stimulating hormone

b Alendronate 70 mg per week, risedronate 35 mg per week, ibandronate (150 mg po monthly or 3 mg iv 3-monthly), zoledronic acid 4 mg iv 6-monthly

c To be given as ≥1 g of calcium + ≥800 IU of vitamin D

d Biochemical markers such as serum C-terminal telopeptide of type I collagen or urinary N-telopeptide of type I collagen

Algorithm 2: Postmenopausal adjuvant treatment with aromatase inhibitors



a Previous low-trauma fracture after age 50, parental history of hip fracture, alcohol intake of ≥4 units/day, diseases associated with secondary osteoporosis, prior corticosteroids for >6 months, low BMI (<22)

b ESR, FBC, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST / γGT), serum creatinine, endomysial antibodies, serum thyroid stimulating hormone

c Alendronate 70 mg per week, risedronate 35 mg per week, ibandronate (150 mg po monthly or 3 mg iv 3-monthly), zoledronic acid 4 mg iv 6-monthly

d To be given as ≥1 g of calcium + ≥800 IU of vitamin D

e Biochemical markers such as serum C-terminal telopeptide of type I collagen or urinary N-telopeptide of type I collagen

7.8 Hormone replacement therapy

HRT, including vaginal administration, is contraindicated for patients on aromatase inhibitors.

HRT may be appropriate for patients on tamoxifen who have low risk of recurrence. This should be only prescribed for relief of vasomotor symptoms at the lowest possible dose for the shortest period to relieve symptoms. Topical, vaginal, administration is appropriate for treatment of vaginal dryness. Decisions should be made on an individual basis, weighing the possible increased risk of recurrence of breast cancer against the beneficial effects on menopausal symptoms.

Progesterone-only preparations should also be considered contraindicated. Because of these theoretical concerns the Mirena® coil is probably not advisable and should be removed.

8. ADJUVANT TRASTUZUMAB

Adjuvant trastuzumab (Herceptin) is recommended as part of adjuvant systemic therapy in HER2+ (IHC 3+ or FISH +) patients. Currently, clinical trial evidence supports the use of trastuzumab with chemotherapy; patients receiving trastuzumab must be fit for, and accept, sequential or concomitant treatment with chemotherapy (a minimum of 4 cycles is generally considered adequate). Advanced age is not in itself a contraindication for trastuzumab but some elderly patients will not be suitable for chemotherapy or have cardiac contraindications to trastuzumab.

HER2+ patients with an indication for trastuzumab should be offered participation in the PERSEPHONE trial.

PERSEPHONE

Main eligibility criteria: HER2 positive early breast cancer with indication for chemotherapy+trastuzumab.

Randomisation:
- Trastuzumab for 1 year (18 doses)
- Trastuzumab for 6 months (9 doses)

Patients who have completed adjuvant trastuzumab should be considered for participation in the Neratinib trial.

NERATINIB (HKI 272)

Main eligibility criteria: HER2 positive, node-positive, completed adjuvant trastuzumab>2 weeks and <1 year from randomization, LVEF>50% , no evidence of recurrence

Randomisation:
- Daily oral neratinib or placebo for 1 year

8.1 Administration

Trastuzumab is given intravenously every three weeks for one year (i.e. a total of 18 doses). The first dose is 8 mg/kg and the following doses 6 mg/kg: actual body weight is used to calculate the dose. New evidence suggests an improved benefit from trastuzumab when given concomitantly with chemotherapy, rather than sequentially after chemotherapy. When anthracycline-free regimens such as TCH or TC are chosen, trastuzumab can be given from the first cycle. In sequential regimens such as AC-D, FEC-D, EpiCMF of ddAC-P trastuzumab can be started after completing the anthracycline part but a new MUGA scan must be obtained in the interval between the last anthracycline dose and the first trastuzumab dose. With other regimens such as FEC or TAC the administration of trastuzumab concurrently with anthracyclines is contraindicated, therefore trastuzumab needs to be delayed until chemotherapy is completed.

8.2 Management of cardiac events in trastuzumab-treated patients

8.2.1 Baseline cardiac assessment prior to cytotoxic chemotherapy

- Medical history & physical examination including BP measurement
    - To detect pre-existing cardiac disease and risk factors.
    - 12-lead electrocardiogram (ECG), with echocardiogram if abnormal
- LVEF measurement using Echo or MUGA scan.

8.2.2 Interventions at baseline

- Referral to a cardiologist
    - recommended for patients with significant cardiac co-morbidity.
- Modification of planned chemotherapy regimen
    - In patients with low or borderline LVEF, an anthracycline-free regimen should be considered
    - Prophylactic ACE inhibitor therapy may also be considered.
- Initiation of ACE inhibitors to control hypertension
    - Hypertension is a potent modifiable risk factor for the development of heart failure during Trastuzumab treatment.
    - Blood pressure above 140/85 mmHg should be treated with an ACE inhibitor, with primary care supervision of dose and renal function
- Lifestyle recommendations
    - Smoking cessation, healthy diet & alcohol intake, optimising weight

8.2.3 Management of cardiac function during trastuzumab

- Assessment of LVEF prior to starting trastuzumab treatment
    - LVEF should be assessed after chemotherapy and before Trastuzumab.
    - Patients with an LVEF >= 50% should start Trastuzumab.
    - Patients with LVEF < 50% should not start Trastuzumab but should be started on an ACE inhibitor and referred to a cardiologist. Repeat assessment of cardiac function should take place after 3 months.
    - Sharp falls in LVEF (> 10 points) during cytotoxic chemotherapy may indicate increased susceptibility to cardiac dysfunction on Trastuzumab. Prophylactic ACE inhibitor therapy may be considered for such patients.
- Routine LVEF monitoring is recommended after 4 and 8 months.
    - Assessment at the end of treatment is recommended for patients requiring cardiovascular intervention during treatment.

- **Patients developing signs and symptoms of heart failure should have their trastuzumab treatment interrupted,** receive an ACE inhibitor and be referred to a cardiologist.
- If the LVEF falls to <=40%, (representing biologically important LV systolic dysfunction) trastuzumab should be interrupted, the patient should receive an ACE inhibitor and be referred to a cardiologist for treatment.
- After Trastuzumab interruption and appropriate medical therapy, LVEF should be re-checked after 6–8 weeks. Trastuzumab may be re-initiated if the LVEF is restored to >50%.
- If the LVEF falls to between 50% and 40%, trastuzumab may be continued, but an ACE inhibitor should be initiated.
    - If the patient is already on an ACE inhibitor, they should be referred to a cardiologist.
    - LVEF assessment should be repeated after 6–8 weeks.
- If the LVEF falls by 10 points or more but remains above 50%, trastuzumab may be continued. Intervention with an ACE inhibitor is recommended in an attempt to reduce the risk of further LVEF decline.
    - LVEF assessment should be repeated after 6–8 weeks.

8.2.4 Traffic light system

Navigation through these guidelines may be facilitated by the adoption of a traffic light system.

- A green light indicates LVEF above 50%, no signs or symptoms of CHF and any trastuzumab-related LVEF fall being less than 10 points.
- An amber light indicates LVEF between 50% and 40%, with no signs or symptoms of CHF, or a trastuzumab-related LVEF reduction of 10 points or more.
- A red light indicates LVEF less than 40% or symptoms and signs of cardiac failure.

Prior to chemotherapy, green indicates go. Red or amber indicates careful consideration of decision to start chemotherapy, with consideration of nonanthracycline- containing regimens. Both amber and red are indications for the initiation of ACE inhibitors, and referral to cardiology for the optimization of cardiac function.

Post chemotherapy, green indicates go. Amber indicates defer until green. Red indicates that it is unlikely to be safe to start trastuzumab. Both amber and red are indications for the initiation of ACE inhibitors and referral to cardiology for the optimization of cardiac function. It is recommended that LVEF is reassessed after 3 months, and that trastuzumab is not commenced unless LVEF is within normal limits at that point.

During trastuzumab, green is an indication to continue treatment. Amber is also an indication to continue chemotherapy, but patients should also be taking an ACE inhibitor. Patients who drop into the amber range while on an ACE inhibitor should be referred for a cardiology opinion. Red is an indication to interrupt trastuzumab, start on an ACE inhibitor (not already taking one) and refer for a cardiology opinion.

Patients whose trastuzumab is interrupted (i.e. red light) should not restart until LVEF is within the normal range (i.e. green light).

8.2.5 Monitoring in metastatic patients

The recommendations, developed for early breast cancer patients, are also suitable for monitoring cardiac effects in metastatic breast cancer patients during the first few months of therapy. After the first 8 months, if no complications have occurred, cardiac monitoring should be performed at the discretion of the treating physician.

9. NEOADJUVANT TREATMENT

Postmenopausal, ER+ patients with early operable breast cancer should be offered participation in the POETIC trial if eligible.

POETIC

Main eligibility criteria: postmenopausal women with ER and/or PgR positive invasive breast cancer on core biopsy, palpable tumour or ultrasound size >=1.5 cm

Randomisation:
- Perioperative therapy: letrozole for 2 weeks before and 2 weeks after surgery
- No perioperative therapy

Subsequent treatments as per standard practice.

Outside trials, neoadjuvant (preoperative) treatment is used in two cases:

- patients who fulfil the criteria for conservative surgery except for tumour size, and desire breast preservation. Neoadjuvant chemotherapy (or letrozole in ER+ postmenopausal patients) may allow conservative surgery in case of response. If this is not achieved within 4 cycles of chemotherapy (or 4 months of hormone therapy), a mastectomy should be considered.

- patients who present with locally advanced, inoperable tumours (mostly T4 and/or N2). Neoadjuvant chemotherapy (or hormone therapy in ER+ patients unfit for chemo) may allow surgery to be performed in case of response.

Standard regimens used in the adjuvant setting can also be used as neoadjuvant treatment: taxane-based regimens are recommended in locally advanced disease. HER2+ patients should also receive trastuzumab as part of their treatment regimen. Response is assessed every two cycles of chemotherapy (or two months of hormone therapy) and surgery performed as soon as feasible. In case of progression, patients are restaged and considered for radiotherapy.

Letrozole is the treatment of choice as primary hormonal therapy in elderly ER+ patients who refuse surgery or are medically unfit for surgery. Limited local surgery under local anaesthetic and/or radiotherapy can also contribute to local control and should be considered after 3-4 months of letrozole.

10. LOCALLY RECURRENT DISEASE

If radical excision of a local recurrence in the conserved breast or in the mastectomy area is not feasible, a biopsy should always be obtained to confirm diagnosis and receptor status (ER, PgR, HER2). Full restaging must include:
- CT scan neck, thorax, abdomen & pelvis
- Bone scan
- FBC, LFTs, U/E, CA 15-3

If restaging is negative, the patient can be treated with curative intent:
- salvage mastectomy if prior conservative surgery
- surgical resection (if feasible) + radiotherapy if prior mastectomy
- radiotherapy if surgery not feasible.

Systemic treatment options after local treatment include:
- hormonal therapy must be instituted or changed in all ER+ patients
- chemotherapy may be considered in selected patients, e.g. those who did not receive adjuvant chemotherapy at diagnosis but would be considered candidate by current criteria
- trastuzumab should be considered in HER2+ patients who did not receive adjuvant trastuzumab.

11. METASTATIC DISEASE

11.1 Restaging

A biopsy of a metastatic lesion should always be considered, if feasible, to confirm diagnosis and obtain ER, PgR and HER2 receptor status if not known. If a biopsy is not performed, ER, PgR and HER2 status must be assessed on the primary tumour if not already known.
Full restaging must include:
- CT scan neck, thorax, abdomen & pelvis
- Bone scan
- FBC, LFTs, U/E, CA 15-3

Magnetic resonance imaging (MRI) is the investigation of choice in cases of:
- suspected spinal cord compression or high risk of cord compression (multiple spinal metastases with back pain)
- suspected brain metastases
- equivocal lesion on an isotope bone scan
- assessment of possible axillary recurrence.

PET-CT should only be used to make a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease.

11.2 General principles of treatment for advanced disease

Although the main objectives of treatment in metastatic breast cancer are symptom control and maintenance of quality of life, an extension of survival can also be obtained with modern systemic therapy.

The following features must be considered to select patients for a specific treatment:
- ER, PgR and HER2 status of primary tumour and, if possible, of metastatic disease
- Previous history of adjuvant therapy
- Disease free interval
- Site and number of metastatic lesions
- Symptoms and performance status
- Rate of progression
- Age, comorbidity and patient's preferences

Patients with ER+, HER2 negative tumours and no aggressive visceral lesions may be treated with one or more lines of hormone therapy before switching to chemotherapy.

Patients with ER negative tumours and those with significant symptoms, or rapidly progressing lesions likely to become symptomatic soon, should be treated with chemotherapy.

Patients with HER2+ tumours must receive trastuzumab (see next section).

11.3 Trastuzumab in advanced disease

All patients with advanced breast cancer should have their HER2 status assessed if not already known.
Patients with HER2+ disease should receive anti-HER2 therapy as part of their treatment, i.e. in combination with chemotherapy, hormone therapy or as single agent. The current standard is trastuzumab + induction chemotherapy followed by maintenance single-agent trastuzumab.
Endocrine therapy can be added after induction chemotherapy in ER+ patients. Trastuzumab + an aromatase inhibitor is an option for HER2+, ER+ patients unfit or unwilling to receive any type of chemotherapy.
Trastuzumab is continued after completion of chemotherapy until progression. In case of development of brain metastases - without extracranial progression - during treatment with trastuzumab, patients are managed with brain radiotherapy or surgery and continuation of trastuzumab. In case of extra-cranial progression, patients are usually offered a new chemotherapy plus continuation of anti-HER2 treatment: this is currently in the form of continuing trastuzumab, but switching to lapatinib is also an option.

Cardiac exclusion criteria and initial monitoring during trastuzumab for advanced disease are as per adjuvant treatment, although given the different prognosis, the balance of risks and benefits should be individualized. If no complications have occurred during the first 8 months of treatment, further cardiac monitoring should be performed at the discretion of the treating physician.

11.4 Hormonal therapy for hormone-responsive advanced disease

The choice and sequence of hormonal therapy for advanced disease depends upon the history of prior treatments. Patients who are premenopausal at the time of relapse must receive ovarian suppression (LHRH analogues, or preferably oophorectomy) as part of their treatment.
Response to hormone therapy must be assessed every 2-3 months and treatment is continued only in case of response or disease stabilization. RECIST criteria should ideally be used. In patients with non-measurable and non-evaluable disease, serial determination of CA 15-3 may help assess the effects of treatment.
The table summarizes local practice for the sequential choice of hormone therapy agents outside clinical trials. The actual choice of a hormonal agent in individual patients may vary depending on personal circumstances, e.g. progestins may be used earlier in patients with anorexia and weight loss, where weight gain is desirable; fulvestrant is administered as a monthly i.m. injection and may be preferred in patients with poor compliance to oral medications.

Prior adjuvant hormone therapy	First line hormone therapy for advanced disease	Second line hormone therapy for advanced disease	Third line hormone therapy for advanced disease
None	Letrozole	Exemestane or tamoxifen	Fulvestrant
Tamoxifen	Letrozole	Exemestane	Fulvestrant
Non steroidal AI (anastrozole or letrozole)	Exemestane or tamoxifen	Fulvestrant	Megestrol
Tamoxifen and exemestane	Letrozole	Fulvestrant	Megestrol
Tamoxifen and non steroidal AI (anastrozole or letrozole)	Exemestane	Fulvestrant	Megestrol
Exemestane	Letrozole or tamoxifen	Fulvestrant	Megestrol

Patients who did not receive adjuvant AIs should receive AIs (letrozole is the local first choice) as first-line. There is no standard first line therapy for patients pre-treated with adjuvant AIs: the table suggests to use the alternative AI (steroidal after non-steroidal, and vice-versa) but tamoxifen is also an option in patients who did not receive tamoxifen as an adjuvant, or received it for a short time.

11.5 Chemotherapy for advanced disease

The choice and sequence of chemotherapy regimens for advanced disease depends upon the history of prior treatments and the HER2 status. The probability of responding to chemotherapy decreases after the first-second line and treatment decisions from this point should be carefully balanced against the risk of causing more side effects than benefits.

Response to chemotherapy must be assessed every 2-3 cycles and treatment is continued only in case of response or disease stabilization. RECIST criteria should ideally be used. In patients with non-measurable and non-evaluable disease, serial determination of CA 15-3 may help assess the effects of treatment. Prolonging chemotherapy beyond 6-8 cycles does not improve overall survival but can prolong the time to progression and may therefore be considered with low-toxicity regimens e.g. oral chemotherapy.

Combination chemotherapy may provide better response rate than single-agent chemotherapy but the survival benefit over sequential use of single agents is uncertain and toxicity is more significant. In patients with rapidly progressing disease, where it is desirable to achieve maximal response quickly, combination chemotherapy is more appropriate than single-agent.

In ER+ patients receiving chemotherapy, hormone therapy is not given concomitantly with chemotherapy. Maintenance hormone therapy after chemotherapy should be offered in ER+ patients in alternative to watchful waiting.

Patients with triple negative tumours and BRCA1/2 mutation carriers should be considered for the TNT trial.

TNT

Main eligibility criteria: metastatic or recurrent locally advanced breast cancer with ER negative, PgR negative (or unknown) and HER2 negative receptor status, or BRCA1/2 mutated with any receptor profile; no prior docetaxel for metastatic disease (adjuvant docetaxel allowed if >12 months from completion)

Randomisation:
- docetaxel 100 mg/m2 q 21 days
- carboplatin AUC 6 q 21 days

Cross-over at progression.

The following tables summarize the local practice of choice and sequence of chemotherapy regimens outside trials.

HER2 negative patients

Prior adjuvant chemotherapy	**First line chemotherapy for advanced disease**	**Second line chemotherapy for advanced disease**
None or CMF	Anthracycline-based	Taxane-based
Anthracycline-based	Taxane-based or anthracycline rechallenge*	Vinorelbine or gemcitabine or capecitabine or alternative taxane**
Anthracyclines and taxanes	Taxane-based (using alternative taxane**) or anthracycline rechallenge*	Vinorelbine or gemcitabine or capecitabine or alternative taxane**

*if >12 months from adjuvant and cumulative dose not reached
** docetaxel if prior paclitaxel and vice-versa

HER2 positive patients

Prior adjuvant chemotherapy	**First line chemotherapy for advanced disease**	**Second line chemotherapy for advanced disease**
None or CMF	Trastuzumab plus taxane	Trastuzumab plus: vinorelbine or gemcitabine or capecitabine or alternative taxane**

Anthracycline-based	Trastuzumab plus taxane	Trastuzumab plus: vinorelbine or gemcitabine or capecitabine or alternative taxane**
Anthracyclines and taxanes	Trastuzumab plus alternative taxane**	Trastuzumab plus: vinorelbine or gemcitabine or capecitabine

** docetaxel if prior paclitaxel and vice-versa. When using trastuzumab + paclitaxel, consider the addition of carboplatin

There are no data on efficacy of restarting trastuzumab at relapse in patients who received adjuvant trastuzumab. Rechallenging with trastuzumab may be appropriate if the treatment-free interval is > 1 year.

11.6 Chemotherapy regimens for advanced disease

Combination regimens:
- AC (doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 day 1 every 21 days)
- Docetaxel + capecitabine (docetaxel 75 mg/m2 day 1 + capecitabine 1 gr/m2 bd day 1-14, every 21 days)
- Paclitaxel + gemcitabine (paclitaxel 175 mg/m2 in 3 hrs day 1 + gemcitabine 1250 mg/m2 in 30 min days 1 and 8, every 21 days).
- Carboplatin AUC 6 plus paclitaxel 175 mg/m2 in 3 hrs day 1 every 21 days in combination with trastuzumab

Single-agent regimens:
- Doxorubicin (60-75 mg/m2 every 21 days)
- Docetaxel (100-75 mg/m2 every 21 days)
- Weekly paclitaxel (80 mg/2 in 1 hr)
- Weekly doxorubicin (20 mg/m2) or epirubicin (25 mg/m2)
- Gemcitabine (1250 mg/m2 days 1 and 8 every 21 days)
- Oral vinorelbine (60 mg/m2 weekly, increased to 80 mg/m2 if well tolerated)
- Capecitabine [1250 mg/m2 bd (1000 mg/m2 bd in patients >60 years old) days 1-14 every 21 days]
- Carboplatin (AUC 6 every 21 days), particularly in triple negative patients not eligible for TNT trial

11.7 New agents

Two new agents have been recently added to Chemocare:
- Nab-paclitaxel as an alternative to paclitaxel or docetaxel, particularly in the following cases:
    - patients with known hypersensitivity to taxanes
    - patients with contraindications to high-dose dexamethasone (diabetes, gastric disorders)
    - patients with intolerance to high-dose dexamethasone (agitation, psychotic symptoms)
- Lapatinib in combination with capecitabine in patients with prior exposure to trastuzumab, where further trastuzumab-based treatment is not considered appropriate.

Bevacizumab in combination with paclitaxel can be considered in selected patients with metastatic breast cancer if funding is available. The main indications, to be discussed within the MDT, are:

- triple negative disease not suitable for the TNT trial
- aggressive or symptomatic disease where it is considered important to maximize the chances of objective response from chemotherapy.

11.8 Surgery in patients with metastatic disease

Resection of the primary breast cancer may be considered in selected patients with metastatic disease:

- when local control will be improved by surgery (e.g. loss of local control with systemic therapy, or high likelihood of loss of control in case of progression). Radiotherapy may be an alternative to surgery in these cases.
- when the patient has oligometastatic disease (e.g. only bone or soft tissue disease, or limited visceral disease well controlled by systemic therapy). Resection of the primary tumour will reduce the total tumour burden and may have an impact on survival.

12. SPECIAL SUBGROUPS OF BREAST CANCER

12.1 Breast cancer in men

Men with breast cancer are staged and treated along the lines of postmenopausal breast cancer in women. Tamoxifen is however the hormone therapy of first choice, since aromatase inhibitors do not suppress testicular production of oestrogens and therefore are of uncertain benefit as single agents (may be used as second-line therapy, in combination with an LHRH analogue).

12.2 Favourable histologies

Patients with pure tubular or colloid breast cancer have a better prognosis; the absolute benefit from adjuvant treatments may be smaller compared to similar patients with ductal or lobular histology.

12.3 Phylloides tumours

Treatment of phylloides tumours is surgical resection with wide margins (1 cm). There is no evidence that adjuvant chemotherapy, hormone therapy or radiotherapy can reduce the risk of local recurrence. After resection of a local recurrence, radiotherapy to the breast or chest wall may be considered.
There is no indication for axillary dissection in phylloides tumours, but staging with chest x-ray is recommended before resection as the lungs are (rarely) a site of metastatic spread. Systemic disease should be treated along the lines of soft tissue sarcomas.

12.4 Paget's disease of the nipple

The majority of patients with Paget's disease of the nipple have an associated in situ or invasive cancer elsewhere in the breast. Surgical treatment may consist of a mastectomy or breast conserving procedure (resection of nipple-areola complex and cancer with negative margins) with axillary sampling or dissection. Breast conserving surgery must be followed by radiotherapy. Systemic adjuvant therapy depends on the characteristics of the invasive component.

12.5 Breast cancer in pregnancy

Diagnostic and staging procedures of breast cancer occurring during pregnancy are the same, with the following exceptions:
- shielding during mammogram and CXR
- staging CT scan and bone scan, if indicated, postponed to the postpartum period.

Breast conserving surgery can be offered if appropriate, but radiotherapy is postponed to the postpartum period.
Chemotherapy may be given, if appropriate, after the first trimester. There is sufficient evidence that anthracycline-based regimens such as FAC are safe for the foetus. Ondansetron and dexamethasone can be used as antiemetics. Foetal monitoring prior to each cycle is recommended. Chemotherapy should be stopped at least 3 weeks before the expected date of delivery.
Hormonal therapy and trastuzumab should not be given during pregnancy.

12.6 Axillary node metastases from unknown primary

Female patients presenting with metastatic carcinoma in axillary lymphnodes and no detectable primary on clinical and radiological staging (which must include bilateral mammogram, whole breast ultrasound, and CT scan neck-thorax-abdomen-pelvis) are treated as node-positive breast cancer with occult breast primary. Contrast enhanced MRI scanning of the breast should be undertaken, as there is evidence that this will reveal the primary tumour in some cases. Surgical therapy of the axilla consists of axillary dissection. Local treatment of the breast may consist of mastectomy or radical radiotherapy. Systemic treatment and radiotherapy recommendations are as in other node-positive breast cancers.

13. BISPHOSPHONATES IN BREAST CANCER

13.1 Malignant hypercalcaemia

Treatment with hydration and intravenous zoledronic acid is normally sufficient to control acute hypercalcaemia in breast cancer. Intravenous ibandronate (at a dose of 2 mg) should be used in patients with severe renal failure (CrCl <30ml/minute).

13.2 Bone metastases

Bisphosphonates should be considered for all breast cancer patients with bone metastases, with the exception of patients having only a limited number of asymptomatic lesions in non-weight bearing bones (e.g. ribs).

Until results of the ZICE trial become available, i.v.zoledronic acid or i.v. ibandronate are the treatment of choice for patients receiving concomitant i.v. chemotherapy or trastuzumab. In patients not receiving other i.v. treatments, oral ibandronate 50 mg od may be offered as an alternative to i.v. bisphosphonates. The duration of therapy depends upon clinical judgement of the balance between benefits for an individual patient, and the risks of renal damage and osteonecrosis of the jaw: patients and their GPs/dentists must be informed about such risks and given recommendations on prevention and early detection. All patients who have received >2 years of i.v.

bisphosphonates should be reviewed periodically to consider alternative options i.e. reduced frequency of infusions, switching to oral ibandronate or cessation of treatment.

Renal function must be routinely assessed before zoledronic acid and doses reduced as appropriate:
- CrCl >60 ml/min = 4 mg
- CrCl 50-60 ml/min = 3.5 mg
- CrCl 40-49 ml/min = 3.3 mg
- CrCl 30-39 ml/min = 3.0 mg
- CrCl <30 ml/min = zoledronic acid contraindicated, consider ibandronate

I.V. ibandronic acid is considered less nephrotoxic. Doses are as follows:
- CrCl >50 ml/min = 6 mg over 15 min.
- CrCl 30-50 ml/min = 6 mg over 1 hour
- CrCl <30 ml/min = 2 mg over 1 hour

14. G-CSFs IN BREAST CANCER

Primary prophylactic (i.e. from cycle 1) use of G-CSF with chemotherapy for breast cancer is recommended in the following cases:
- Chemotherapy regimens with >20% predicted risk of febrile neutropenia (FN)
- Chemotherapy regimens with 10-20% risk of FN in the presence of patient-related risk factors, e.g. age≥65, advanced disease

After an episode of FN, **secondary prophylactic** use of G-CSF is recommended for patients receiving adjuvant chemotherapy. Dose-reduction should be considered in patients receiving palliative chemotherapy for metastatic disease.

G-CSF treatments include pegfilgrastim 6 mg s.c given once per cycle 24 hours after chemotherapy and filgrastim 5 mg/kg s.c. given daily for 8-10 days covering the time of the expected nadir, e.g. on days 3-10 for docetaxel-based regimens. For chemotherapy regimens where cytotoxic agents are given at intervals shorter than 14 days (e.g. weekly chemotherapy), pegfilgrastim is not suitable and daily G-CSF should be used, avoiding the administration of chemotherapy and G-CSF at less than 24 distance from each other.

Patients with febrile neutropenia should not be routinely given G-CSF as adjunct therapy to antibiotics and supportive care, unless there are high-risk factors (advanced age, severe comorbidity, organ dysfunction, hypotension).

15. FOLLOW UP

15.1 Hospital-based follow up

Hospital-based follow up of early breast cancer patients who have completed chemotherapy, radiotherapy and trastuzumab is aimed mainly at:
- early detection of potentially curable events (locoregional recurrence, contralateral breast cancer)

- monitoring of side effects and compliance to adjuvant hormone therapy in HR+ patients
- monitoring of bone health according to NCRI guidelines.

15.2 Mammograms

Mammograms are recommended as follows:

After breast conservation:
- Annual bilateral mammogram yearly for 5 years
- After year 5:
    - patients over the age of 50 enter BTW screening program (mammogram every 3 years)
    - patients under the age of 50 continue with yearly mammogram until they reach 50
    - patients over 70 are encouraged self referral to BTW every 3 years.

After mastectomy:
- contralateral mammogram at year 1, 3 and 5 post-mastectomy
- After year 5:
    - patients over the age of 50 enter BTW screening program (mammogram every 3 years)
    - patients under the age of 50 continue with mammogram every 2 years until they reach 50
    - patients over 70 are encouraged self-referral to BTW every 3 years.

15.3 Other investigations

- Routine radiology, bone scans or markers are not recommended in asymptomatic patients during follow up.
- Endometrial monitoring (with ultrasound) is not recommended during tamoxifen in asymptomatic patients. Patients must however be educated about the need to report symptoms promptly.
- Postmenopausal patients with vaginal bleeding during tamoxifen must be investigated with a hysteroscopy; ultrasound scans or pipelle biopsies are not sufficient to exclude cancer in this setting. Benign tamoxifen-associated endometrial changes (glandulocystic atrophy, polyps) may normalise after switching to an AI. Patients with pre-neoplastic or neoplastic findings must be referred to the Gynae Oncology MDT.

16. REFERRAL TO CANCER GENETICS

Within the management of breast cancer it is important that all women with breast cancer are asked if they have either a maternal or paternal family history of breast and or ovarian cancer. If so, they should be assessed against the Cancer Genetics Service for Wales Guidelines and offered referral to the Cancer Genetics Service if appropriate.

Patients with breast cancer are eligible for referral in the following cases:

- male sex
- bilateral breast cancer
- age at diagnosis 40 or under
- age at diagnosis 60 or under, if another first or second degree relative had breast cancer diagnosed at 60 years or less
- 2 first or second degree relatives with breast cancer on the same side of the family, diagnosed at any age
- concomitant ovarian cancer
- age at diagnosis 50 or under, with a first degree relative with ovarian cancer.

Any member of the multidisciplinary team can make referrals to the Cancer Genetics Service for Wales, but it is important that a key professional takes responsibility to ensure eligibility for a cancer genetics assessment is not overlooked.

Patients with advanced breast cancer who are BRCA1/2 mutation carriers may be eligible for the TNT trial (Section 11.5)

17. PSYCHOLOGICAL SUPPORT

Many women will undergo a period of distress following diagnosis, or other bad news relating to treatment. Most will not require formal psychological treatment, although many will appreciate informal support.

Some possible predictors of poor psychological adaptation are:

- advanced disease
- other concurrent stress / illness
- lack / unavailability of personal support
- hopelessness
- previous or current psychiatric problems including depression
- overly intense emotional investment in breasts.

Consider support / interventions on 3 levels:

Level 1 - for most women, explanation and information, provided by ward and community staff, and supplemented by friends/family, is all that is required. This should be specifically incorporated into nursing care plans. Nursing and medical staff should make a point of enquiring about concerns, and screen for more significant psychological needs (see below). Consider providing printed self help materials and references. Consider training for staff in this area.

Level 2 - Counselling and skilled support
e.g. Primary Care counseling, non-statutory / charitable support such as CISS (Swansea), Maggie's Centre, etc. Some Breast Care Nurses receive support / supervision from counsellors to undertake this work. Some hospitals train volunteers in counselling. Teams should compile lists of resources available in their area.

Lever 3 - more formalised psychological / psychiatric treatments

For those with moderate - severe depression, patients who express clear suicidal intent, also those who worsen despite the above approaches. Screen with HAD Scale (Hospital Anxiety and Depression Scale, Zigmond & Snaith) - scores of 11 or more on either Depression or Anxiety subscale suggest may benefit from referral. Discuss more unusual reactions e.g. denial which is more than short-lived; marked body image disorder, etc. Teams should compile local referral pathways, as there is some evidence that patients with cancer find it difficult to access these services.