

**Clinical Management Protocol – Chemotherapy – Breast Cancer**

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**Protocol for Planning and Treatment**

The process to be followed when a course of chemotherapy is required to treat:

**BREAST CANCER**

**Patient information given at each stage following agreed information pathway**

<p><b>1. DIAGNOSIS</b></p> <p>Diagnosis will usually be confirmed – by core biopsy of the primary tumour</p>
<p><b>2. STAGING</b></p> <p>Staging for distant metastases will only be undertaken if patients are either</p> <ol style="list-style-type: none"><li>Symptomatic</li><li>Asymptomatic but have either a locally advanced tumour T3/4 &amp;/or N2 at presentation or have a NPI score of 5.5 or more postoperatively</li></ol>
<p><b>3. HISTOPATHOLOGY</b></p> <p>Invasive Breast carcinoma</p>
<p><b>4. RADIOTHERAPY</b></p> <p><b><u>After Surgery to the Breast</u></b></p> <p><b>a) After wide local excision or quadrantectomy of the tumour</b></p> <p>Radiotherapy reduces the risk of local recurrence by about two-thirds even if the patient has systemic adjuvant therapy. The local protocol for radiotherapy is:</p> <ul style="list-style-type: none"><li>Whole breast: 40Gy to whole breast in 15 fractions</li><li>16Gy boost in 8 fractions over 10-12 days for those aged 44 years and under</li><li>10Gy boost in 5 fractions over 5-7 days for those aged 45-54 years</li><li>No boost (unless specifically indicated, e.g. involved margins) for those aged 55 years and over</li><li>Large breasts: for the small number of women with very large breasts, where radiotherapy is either not possible or likely to be associated with considerable morbidity, external beam radiotherapy to the tumour bed only may be given (45-55Gy in 20-25 fractions, depending whether the same fields used for the boost as for the main fields) [recurrences occur most commonly within or close to the tumour bed.]</li></ul>

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CSBS Standard: 85% of patients will receive radiotherapy to the breast after wide local excision for invasive cancer

### **b) After mastectomy**

Radiotherapy after mastectomy reduces the risk of local recurrence by about two-thirds. The absolute benefit of radiotherapy is relatively higher in those cases at highest risk of local recurrence; for example, larger tumours (>5 cms), those with involved (usually deep) margins and/or those with poor prognostic features (higher grade, node positive, vascular/lymphatic invasion). Conversely, the benefit of radiotherapy in terms of local control, is less for patients with favourable prognostic features and hence it is not recommended for these patients.

### **After Surgery to the Axilla**

#### **Summary of Axillary Management**

If N-, no further axillary treatment (note: regard isolated tumour cells only as node negative)

After sentinel node biopsy (SNB): if N+, either axillary clearance or axillary radiotherapy.

Axillary Sample (at least 4 nodes): If N+, either axillary clearance or axillary radiotherapy

If N-, no further axillary treatment

Axillary Clearance

If N+, no further axillary treatment

#### **Notes:**

Axillary sampling: If the sample is inadequate (i.e. 3 or less nodes), the axilla should normally be irradiated.

Axillary clearance: After axillary clearance, the axilla should not be routinely irradiated. For patients with nodal involvement by tumour (N+) where the nodes were adherent to the axillary vein or there were obvious nodes palpable above the dissected nodes, then the potential benefits of radiotherapy in reducing the risk of local recurrence must be balanced against the risks of morbidity.

CSBS Standards: Essential: 85% of patients receive radiotherapy to the axilla after a node positive node sample (desirable 95%)

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### Supraclavicular Fossa

The ipsilateral supraclavicular fossa is not normally managed surgically. The role of adjuvant radiotherapy is not clear. Spread to the supraclavicular fossa is regarded as metastatic disease, and trials have not clearly demonstrated whether adjuvant supraclavicular fossa irradiation reduces the risk of metastatic spread.

For the small number of patients with proven spread to the supraclavicular fossa, but without evidence of spread to other distant sites, it may be appropriate to give radiotherapy to the supraclavicular fossa in a bid to improve local control.

For patients with small, node negative disease who have had breast conservation, supraclavicular fossa irradiation is not indicated. In contrast, for patients who have evidence of significant axillary nodal spread (e.g. at least 4 nodes involved), then supraclavicular fossa irradiation may be given, since such patients are probably at increased risk of relapse in the supraclavicular fossa. The dose schedule is as for postmastectomy irradiation and the fields should avoid the axilla if it has been cleared.

**For all chemotherapy patients ([neo-]adjuvantly and palliatively) the regimens are as defined in Chemocare.**

## 5. SYSTEMIC THERAPY

### Chemotherapy

#### a) Neoadjuvant chemotherapy

Locally advanced breast tumours (T3/4 or N+, or T2 tumours within a small breast) may benefit from neoadjuvant (primary) chemotherapy which may in some circumstances facilitate breast-conserving surgery, if this is the patient's preference. At present there is no definitive evidence of survival benefit compared to adjuvant therapy, therefore a decision should be made on an individual basis. The patient should be counselled that there can be no guarantees about the possibility of conservation surgery.

It should be clear from the core biopsy pathology results (and any pertinent patient factors eg age, fitness) that the patient would be routinely offered adjuvant chemotherapy before neoadjuvant chemotherapy can be considered.

Patients with triple receptor negative (TNBC), ER negative, grade 3 or HER-2 positive breast cancers are most likely to benefit from a neoadjuvant approach.

All patients being offered neoadjuvant chemotherapy should receive an anthracycline and a taxane, if fit enough. A MUGA scan is required at baseline and again after 3 cycles if a patient is being planned for trastuzumab therapy.

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### Suitable regimens:

Standard regimen: FEC-T

5-FU 500mg/m<sup>2</sup> iv bolus day 1 q21 days cycles 1 - 3

Epirubicin 75mg/m<sup>2</sup> iv bolus day 1 q21 days cycles 1 - 3

Cyclophosphamide 500mg/m<sup>2</sup> iv bolus day 1 q21 days cycles 1 - 3

THEN

Docetaxel 75mg/m<sup>2</sup> for cycle 4, increased to 100mg/m<sup>2</sup> if adequately tolerated q21 days cycles 5 – 6 with pegylated GCSF 6mg on Day 2

Trastuzumab should be added with docetaxel cycles for all patients who are HER-2 positive, unless there are compelling cardiac contra-indications. Trastuzumab has been shown to significantly increase the complete response rate when given with neoadjuvant chemotherapy.

Deviations from standard:

- For elderly patients or those of poor PS who are deemed unsuitable for the standard regimen, a combination of 3 cycles of EC (Epirubicin 75mg/m<sup>2</sup> and Cyclophosphamide 600mg/m<sup>2</sup> q21 days) followed by weekly paclitaxel 80mg/m<sup>2</sup> for 9 weeks can occasionally be used if patient is not fit enough for FEC-T.
- Very occasionally (if patient has inoperable ER-ve disease and anthracyclines are contraindicated), weekly paclitaxel can be given with or without trastuzumab to unfit patients.
- Patients will usually receive six cycles of chemotherapy before being considered for surgery. Tumour response should be assessed radiologically with an MRI (unless contra-indicated) with baseline scan, followed by repeat MRI after cycles 2 and 6, with assessment in consultant's clinic after cycle 3 and discussion in MDM at cycle 6.
- No further chemotherapy will be given post-operatively unless within the context of a clinical trial. Trastuzumab will be continued as single agent for a further 15 cycles q21 days with cardiac monitoring every 4 months.

### b) Adjuvant chemotherapy

All patients, without evidence of distant metastases and who have had primary surgery for invasive breast cancer, should be considered for systemic adjuvant therapy.

The Overview of randomized trials of polychemotherapy for early breast cancer shows an absolute 10-year survival benefit in women under 50 years old with node positive disease of around 11% and node negative disease 7%. (See *Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet. 2012*)

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**Risk assessment**

The risk of systemic relapse can be partially quantified using the Nottingham Prognostic Index (NPI)

NPI = Grade I II III + Nodes 0 1-3 >3 + pathological size  
Points 1 2 3 1 2 3 cm x 0.2

NPI score: <3.4 good prognosis

NPI score: 3.4 – 5.4 intermediate prognosis (<4.4 low intermediate, >4.4 high intermediate)

NPI score: >5.4 poor prognosis

Importantly, the NPI does not however take into account other poor prognostic biological features such as HER-positivity or TNBC and so this also needs to be taken into account.

**Pre-menopausal patients**

Young patients have a higher risk of relapse, particularly the <35 group.

ER +ve : low risk - Tamoxifen only

ER +ve : medium risk (NPI intermediate, other poor prognostic factors) - Tamoxifen and consider chemotherapy (decide individually but would for example include those with a >5% benefit in 10 year survival on adjuvant online)

ER +ve : high risk (NPI high intermediate or high) - Tamoxifen and elective chemotherapy.

All methods of ovarian ablation seem to be equally effective - surgical (open or laparoscopic), oophorectomy, radiation menopause or LH-RH agonist (latter for at least 2 years).

The benefit of hormonal management is low in ER-ve patients, and hormonal adjuvant therapy is not recommended in these patients, unless they are Progesterone receptor (Pg) +ve where some data indicates they may benefit from hormonal therapy as for ER +ve patients above

ER –ve : low risk (NPI low) - no systemic adjuvant therapy

ER –ve : medium risk (NPI intermediate, poor prognosis biology) - adjuvant chemotherapy

ER –ve : high risk (NPI high) - adjuvant chemotherapy

**Post-menopausal patients**

ER +ve : low risk (NPI low or low intermediate) - Tamoxifen or AI (see below) only

ER +ve : medium risk (NPI intermediate and/or poor prognosis biology) - Tamoxifen or AI (see below) ± chemotherapy (decide on individual bases but would for example

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include those with a >5% benefit in 10 year survival on adjuvant online)  
ER +ve : high risk (NPI high intermediate or high, poor prognosis biology) - usually an AI and, if fit, elective chemotherapy.

### Definition of Low Risk

In this category, the absolute survival benefit for adjuvant chemotherapy is either unproven or so small as to be not clinically recommended:

- Patients with all of the following (St Gallen, 2007)
- Lymph node negative and all of the following:
  - Tumour  $\leq$  2cms
  - ER and/or PR expressed
  - Grade I histology
  - No peri-tumoral vascular invasion
  - Age  $\geq$ 35 years
  - Her2 negative

### Patients Eligible for Adjuvant Chemotherapy

Any patient who is not at low risk may require a discussion regarding adjuvant systemic treatment. As a general guideline, the greater the number of poor prognostic factors, the greater the risk and the stronger should be the recommendation for chemotherapy.

Patients with some/any of the following may be at sufficient risk to offer adjuvant chemotherapy on the basis of established survival benefits (*St Gallen Guidelines, 2007*). For each patient the pros and cons of this treatment need to be discussed.

The *Adjuvantonline* web-based system can be helpful to estimate of potential benefit of adjuvant chemotherapy, but again this does not incorporate other biological subtypes which are at higher risk of relapse, and so can underestimate the risk of relapse and potential benefit.

### Intermediate Risk

- Node negative AND at least one of the following features:
  - pT > 2 cm OR
  - Grade 2-3 OR
  - Presence of extensive peritumoral vascular invasion OR
  - ER and PgR absent OR
  - HER2 positive OR
  - Age < 35 years
- Node positive (1–3 involved nodes) AND
  - ER and/or PgR expressed AND
  - HER2 negative

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**High Risk**

- Node positive (1–3 involved nodes) AND
  - ER and PgR absent, OR
  - HER2/*neu* gene over expressed or amplified
- Node positive (4 or more involved nodes)

**c) Choice of chemotherapy regimen**

FEC-T to be considered for all patients with any of:

- Involved axillary lymph nodes
- HER-2+ cancer  $\geq$ T1b
- Triple negative breast cancer
- Pre-menopausal status
- Other poor prognostic feature (eg extensive LVI), at discretion of consultant

5-FU 500mg/m<sup>2</sup> iv bolus day 1 q21 days cycles 1 - 3

Epirubicin 75mg/m<sup>2</sup> iv bolus day 1 q21 days cycles 1 - 3

Cyclophosphamide 500mg/m<sup>2</sup> iv bolus day 1 q21 days cycles 1 – 3

THEN

Docetaxel 75mg/m<sup>2</sup> for cycle 4, increased to 100mg/m<sup>2</sup> if adequately tolerated q21 days cycles 5 – 6 with pegylated GCSF 6mg on Day 2

A combination of 3 EC followed by weekly paclitaxel for 9 weeks is occasionally used if patient is not fit enough for FEC-T, but the benefits of treatment outweigh the risks.

If a patient commences adjuvant docetaxel q21 days but has significant (usually G3) toxicity, occasionally weekly paclitaxel can be substituted for the remainder of the proposed treatment.

FEC 75 x 6 for other lower risk patients:

- Consider in patients  $\geq$ 50years with ER positive HER-2 negative node negative disease
- No other compelling risk factors e.g. extensive LVI

5Fluorouracil 500mg/m<sup>2</sup> iv bolus day 1 q21 days cycles 1 – 6

Epirubicin 75mg/m<sup>2</sup> iv bolus day 1 q21 days cycles 1 – 6

Cyclophosphamide 500mg/m<sup>2</sup> iv bolus day 1 q21 days cycles 1 – 6

All patients receiving FEC75 x 6 should be considered for a PICC line at the start of treatment, unless there are contraindications. Patients should be counselled regarding the risk of line-associated infection and thrombosis.

TC x 4 for less fit patients or those with contraindications to anthracyclines; e.g. cardiac contra-indications, prior anthracycline treatment for other primary cancer, or

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patients for trastuzumab where cardiac compromise to be avoided e.g. baseline LVEF < 55%:

Docetaxel 75mg/m<sup>2</sup> iv infusion day 1 q21 days cycles 1 - 4  
Cyclophosphamide 600mg/m<sup>2</sup> iv bolus day 1 q21 days cycles 1 – 4  
Note four cycles only.

### Anti-HER2 targeted therapy

Patients with HER2-positive tumours are thought to have up to 2.7 times the rate of recurrence and 5.3 times the rate of distant recurrences at 5 years compared with HER-2 negative tumours (*Gonzalez-Angulo JCO 2009*).

Patients who are HER2 +ve (confirmed with FISH), who are also suitable for adjuvant chemotherapy, should be given 18 cycles of adjuvant trastuzumab therapy for one year, unless there is a compelling reason not to. The decision to treat should be made at consultant level. There is no evidence at present that patients should receive adjuvant trastuzumab without chemotherapy. Consideration should also be given to entry to clinical trials where appropriate.

### Cardiac screening/monitoring

A MUGA scan will be requested prior to commencement of chemotherapy in all patients who are to receive an anthracycline or those planned to receive adjuvant trastuzumab.

It is acceptable for the MUGA scan to be performed prior to cycle 2 in most patients but for those with cardiac risk factors or when required within a trial protocol, the MUGA should be performed before cycle 1.

The normal clinical cut-off value for the MUGA will be 55%. Patients with values below this level should be reviewed and only proceed with either anthracycline chemotherapy or trastuzumab if it is felt that the anticipated clinical benefits outweigh the risk to the myocardium. This will be decided on a case by case basis, normally at consultant level.

### GCSF

This will only be used routinely as primary prophylaxis for patients receiving neoadjuvant or adjuvant docetaxel 100mg/m<sup>2</sup>. There is, however, good evidence that when used for secondary prevention, it can decrease the need for hospital admissions with neutropenic fever and also increase dose intensity by allowing chemotherapy to be given on time. In patients receiving non-docetaxel adjuvant chemotherapy, who have an admission for neutropenic fever/sepsis, have more than one dose delay, or neutrophils 1.0-1.5 on treatment day should be prescribed GCSF for all subsequent cycles.

For patients with slow wound healing which is delaying the initiation of adjuvant

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chemotherapy, but who are otherwise deemed fit to proceed, occasionally a once-off dose of pegylated GCSF with cycle 1 can be prescribed as primary prophylaxis.

**Endocrine Therapy**

For all newly diagnosed postmenopausal patients

Definition of Patient Group	Adjuvant Hormone Strategy
Very low risk NPI $\leq$ 3.4 AND node negative	Tamoxifen for 5 years
All ER &/or PR+ve Contra-indication. to tamoxifen	Immediate AI anastrazole or letrozole  Duration 5 years

**Extended adjuvant therapy**

The MA17 trial indicates that extended adjuvant therapy with letrozole can reduce the risk of recurrence in higher risk patients, where there may be a survival advantage. Post menopausal patients who were originally node positive and have completed 5 years of adjuvant endocrine therapy should be considered for extended adjuvant therapy with letrozole, ideally within the SOLE trial.

In the extended adjuvant setting, post-menopausal includes:

- pre-menopausal women who have entered the menopause during chemo or while on tamoxifen, are >50yrs old and have remained amenorrhoeic for > 1 year (no previous hysterectomy)
- any woman with prior surgical/radiation induced menopause (bilateral oophorectomy/bilateral ovarian radiation) and, for the radiation patients, FSH/LH and oestradiol blood levels within the post menopausal range

Excluded from AI therapy are:

- Any pre-menopausal patient
- Any pre-menopausal woman who has entered the menopause during chemo or while on tamoxifen who is  $\leq$ 50yrs old **UNLESS** they undergo surgical/radiation induced menopause (bilateral oophorectomy/bilateral ovarian radiation) and, for the radiation patients, FSH/LH and oestradiol blood levels within the post menopausal range are obtained and are consistently in the postmenopausal range (when off tamoxifen)

Contra-indications to use of AI's /extended adjuvant letrozole are to be decided on an individual basis but include:

- Significant cardio-vascular disease
- Significant (clinically evident) osteoporosis

All patients starting an AI should have a DEXA scan to assess bone density (unless

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already on a bisphosphonate). If found to be osteoporotic or significantly osteopenic, then they should be recommended to take a bisphosphonate and calcium and vit D supplements (whilst on the AI for osteopenic patients).

Current trials ongoing or in early follow up looking at the issue of adjuvant aromatase inhibitors are:

- ATAC Arimidex, Tamoxifen alone or in combination.
- MA-17 Tam. for 5 yrs +/- Letrozole or placebo for 3yrs
- IES Tam. x 2-3 yrs then tam. x 2-3yrs or exemestane x 2-3yrs
- ITA Tam. x 2-3yrs then tam. x 2-3yrs or anastrozole x 2-3yrs
- ARNO/ ABCSG 8 Tam. x 2 yrs then tam. x 3yrs or anastrozole x 3yrs
- BIG1-98 Tam. vs Letrozole vs Tam. then letrozole vs Letrozole then tam
- TEAM Tam. x 2.5-3yrs then exemestane to 5 yrs vs Exemestane x 5yrs

For patients in whom tamoxifen is contra-indicated (history of venous thrombo-embolism, endometrial abnormalities), anastrozole/letrozole should be prescribed instead. Similarly, for patients who are prescribed tamoxifen but have significant problems tolerating it, anastrozole/letrozole is an alternative if it is judged the patients have a continued need for adjuvant hormonal therapy. (Note AI's should only be prescribed to postmenopausal women).

Patients whose periods stop during adjuvant chemotherapy should generally still be considered premenopausal since periods can return even up to several years later.

The benefit of hormonal management is less clear in ER-ve patients, and hormonal adjuvant therapy is not recommended in these patients, unless they are Pg+ve where preliminary data indicates they may benefit from hormonal therapy as for ER+ve patients above.

ER –ve : low risk (NPI low) - no systemic adjuvant therapy

ER –ve : medium risk (NPI intermediate) - adjuvant chemotherapy, consider anthracycline based chemotherapy for patients who are fit

ER –ve : high risk (NPI high) - adjuvant chemotherapy using anthracycline based regime, such as FEC75 if fit

QPI Standards: All women with invasive breast cancer are considered for adjuvant systemic therapy

Essential: 85% of patients with ER +ve, node +ve tumours receive adjuvant hormonal therapy (desirable 95%)

Essential: 85% pre- or peri-menopausal women with ER –ve, node +ve tumours receive adjuvant chemotherapy (desirable 95%).

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**Systemic Therapy in Locally Recurrent Breast Cancer**

Consider adjuvant chemotherapy and/or endocrine therapy after complete surgical excision of local recurrence. Treatment options will depend on time from primary treatment, prior drug exposure and ongoing toxicities.

It is important to discuss that there is only limited evidence that adjuvant chemotherapy can significantly improve DFS and OS in patients with locally recurrent disease. This effect appears to be confined to patients with ER-ve disease. (Aebi, Proc SABCS 2012)

**Metastatic Disease**

**a) Systemic endocrine therapy**

All patients with metastatic disease should be considered for systemic therapy. The appropriate treatment will be mainly determined by hormone receptor status

If ER+ve, and no visceral disease (e.g. liver mets or lymphangitis carcinomatosa)  
Start with hormonal therapy (influenced by previous adjuvant hormone therapy).  
If premenopausal, consider ovarian ablation (usually LH-RH agonist)

Otherwise, treat in sequence: aromatase inhibitor (anastrozole, letrozole, exemestane – no comparative data), tamoxifen, megestrol acetate  
[remember, cannot use aromatase inhibitors in premenopausal patients (unless on LH-RH agonist)]

Choice of appropriate endocrine agent (depends on menopausal status and on previous adjuvant therapy)

As for adjuvant, although aromatase inhibitor may be used first-line for post-menopausal patients.  
Megace a useful third line agent.

<b><i>Pre-menopausal</i></b>	<b><i>Post-menopausal</i></b>
ovarian ablation	aromatase inhibitor
ovarian ablation + aromatase inhibitor	tamoxifen
megace	megace

For the small number of patients who still have hormone sensitive disease after use of the above agents (or in whom compliance is deemed to be a significant problem), faslodex can be used (requires specific authorisation by a consultant).

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**b) Palliative chemotherapy**

Palliative chemotherapy is usually given to control disease and palliate symptoms. The decision to initiate palliative chemotherapy is usually made in conjunction with a consultant.

Always consider entry into available clinical trials. The choice of palliative chemotherapy regimen depends on a number of factors; patient's fitness, organ function and preferences, time from primary or previous treatment, previous treatment response, prior drug exposure and ongoing toxicities.

First line chemotherapy for metastatic disease is usually with a taxane regime (eg in those with prior anthracyclines, HER2 status positive or unknown) or an anthracycline regime (eg in those with no prior anthracyclines and HER2 negative).

While sequential single agent treatment is generally favoured in the metastatic setting, some patients who require a rapid response to therapy may benefit from a combination regime. Trastuzumab is usually started with first line taxane or vinorelbine chemotherapy in HER-2 positive cancers. Concurrent administration of trastuzumab with anthracyclines is not recommended. If the patient responds, trastuzumab will be continued indefinitely after completion of chemotherapy until unacceptable toxicity or progression.

Capecitabine may be used as an alternative, especially for patients who are less fit or who have bone marrow infiltration. For the small number of patients with good performance status and ongoing disease in whom active treatment is appropriate, docetaxel and capecitabine may be used in sequence and vinorelbine as a further alternative.

For a small number of patients with ER/Pg/HER2 negative cancers, especially if of medullary subtype or young and with a strong family history or known BRCA1/2 mutation, there is some evidence to suggest platinum (usually carboplatin as is better tolerated) may be a useful agent. For these patients platinum may be considered as an alternative to taxanes or capecitabine, after discussion with consultant.

**Suitable regimens for palliative chemotherapy:**

Commonly used regimens:

- Docetaxel 75mg/m<sup>2</sup> increased to 100mg/m<sup>2</sup> if well tolerated q21 days
- Epirubicin 75mg/m<sup>2</sup> q21 days (usually if no prior anthracycline)
- Capecitabine 1250mg/m<sup>2</sup> q21 days
- Vinorelbine oral or IV q7days

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Less commonly used regimens:

- Carboplatin AUC5-6 q21 days (BRCA1/2, TNBC or medullary cancers)
- Weekly paclitaxel 80mg/m<sup>2</sup> q 7 days (only for patients not fit enough for 3-weekly docetaxel only)
- EC (Epirubicin 75mg/m<sup>2</sup> and cyclophosphamide 600mg/m<sup>2</sup>) q 21days
- Weekly epirubicin (variable dose; for severe liver impairment)
- Clinical trial protocol therapy

Assessment of response

Response to treatment should usually be assessed after every third cycle (or nine weeks), and most patients will receive six cycles of chemotherapy if responding. Some patients may benefit from continuing with capecitabine longer term, until progression or unacceptable toxicity, if they are shown to have ongoing response and the drug is well tolerated.

Toxicity assessment

Toxicity should be assessed at every cycle, so that doses may be modified or discontinued as appropriate. Dose intensity does not significantly alter survival in metastatic disease.

GCSF

GCSF should not normally be used in patients receiving palliative chemotherapy, where a dose reduction is appropriate if there is toxicity. For a small number of patients with good performance status, judged to be likely to have a good response to chemotherapy, but have problems with marrow toxicity (especially with taxanes) then GCSF may be used provided two consultants agree it is appropriate.

### c) Bisphosphonates

For patients with established bony metastatic disease, bisphosphonates can reduce bone morbidity – pathological fractures, bony pain and the need for palliative radiotherapy. Ibandronate 50 mg. daily po is the current standard therapy. If intolerant, either IV pamidronate or zoledronate should be considered.

Occasionally for patients with a heavy burden of bone metastases or at high risk of skeletal events, but who have intolerance/contraindication to all bisphosphonates, subcutaneous denosumab can be occasionally considered. There is an established NHS Tayside shared care protocol for osteoporosis with GPs for later treatment in the community.

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