Chemotherapy Protocol

BREAST CANCER

CARBOPLATIN (AUC6)-DOCETAXEL-TRASTUZUMAB (TCH)

Regimen

- Breast Cancer – Carboplatin (AUC6)-Docetaxel-Trastuzumab (TCH)

Indication

- Adjuvant treatment of high risk (node positive or negative tumour greater than or equal to one centimetre) HER2 positive breast cancer that has failed to adequately respond to an anthracycline containing therapy or where anthracycline therapy is contra-indicated.

- WHO Performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Carboplatin	Neuropathy, nephrotoxicity, ototoxicity, thrombocytopenia
Docetaxel	Hypersensitivity, fluid retention, neuropathy, joint pains, nail changes, fatigue, alopecia, neutropenia
Trastuzumab	Cardiotoxicity, acute respiratory distress syndrome, infusion related effects

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Regimen

- FBC, U&E's and LFT's prior to each cycle

- EDTA or calculated creatinine clearance before the first cycle

- HER2 status prior to initiating therapy

- Cardiac function must be assessed prior to starting trastuzumab. Thereafter in the adjuvant setting it should be assessed every 12 weeks unless there is clinical evidence of cardiac failure. In the metastatic setting cardiac function should be assessed every 12 weeks for 24 weeks then every 24 weeks thereafter, again, unless there is clinical evidence suggestive of cardiac failure

- Blood pressure prior to each trastuzumab administration

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances. This is especially true in the adjuvant / neoadjuvant setting where dose delays and reductions may be less appropriate. The following is a general guide only.

Haematological

Prior to prescribing the following treatment criteria must be met;

Criteria	Eligible Level
Neutrophils	equal to or more than $1x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL

If counts on day one are below these criteria for neutrophil and/or platelets then delay carboplatin and docetaxel treatment for seven days. Only re-start treatment when these levels are reached. If patients experience a febrile neutropenia or a treatment delay due to neutrophil count of less than 0.5 $x10^9$/L or platelets less than 50 $x10^9$/L for more than seven days, then reduce the dose of carboplatin and docetaxel to 80% of the original dose. If the neutropenia or thrombocytopenia recurs despite this decrease in dose intensity, the dose should either be further reduced to 50% of the original dose or treatment stopped.

Haematological dose modifications are not necessary for trastuzumab. If patients do not tolerate trastuzumab it should be stopped. These modifications refer to carboplatin and docetaxel only.

Liver Impairment

<table>
<tr><th>Drug</th><th>Bilirubin (µmol/L)</th><th></th><th>AST/ALT (units)</th><th></th><th>Alk Phos (units)</th><th>Dose (% of original dose)</th></tr>
<tr><td>Carboplatin</td><td colspan="6">No dose adjustment needed</td></tr>
<tr><td rowspan="2">Docetaxel</td><td>N/A</td><td></td><td>1.5xULN or greater</td><td>and</td><td>2.5xULN or greater</td><td>Consider 75%</td></tr>
<tr><td>Greater than ULN</td><td>and/or</td><td>3.5xULN or greater</td><td>and</td><td>6xULN or greater</td><td>Not Recommended</td></tr>
<tr><td>Trastuzumab</td><td colspan="6">No dose adjustment needed</td></tr>
</table>

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Carboplatin	20ml/min or less	Contra-indicated
Docetaxel	No dose adjustment necessary	
Trastuzumab	No dose adjustment necessary	

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Docetaxel

Peripheral neuropathy at NCI-CTC grade 3 should result in a dose reduction from 75mg/m^2 to 60mg/m^2. If the NCI-CTC grade 3 neuropathy occurred at doses lower than 75mg/m^2 or a NCI-CTC grade 4 toxicity develops stop treatment.

Excessive tearing / lacrimation are related to cumulative docetaxel doses and occur after a median of 400mg/m^2. Symptomatic treatment with hypromellose 0.3% eye drops four times a day may help. However, if the ocular irritation continues reduce the docetaxel dose to 60mg/m^2 in the first instance.

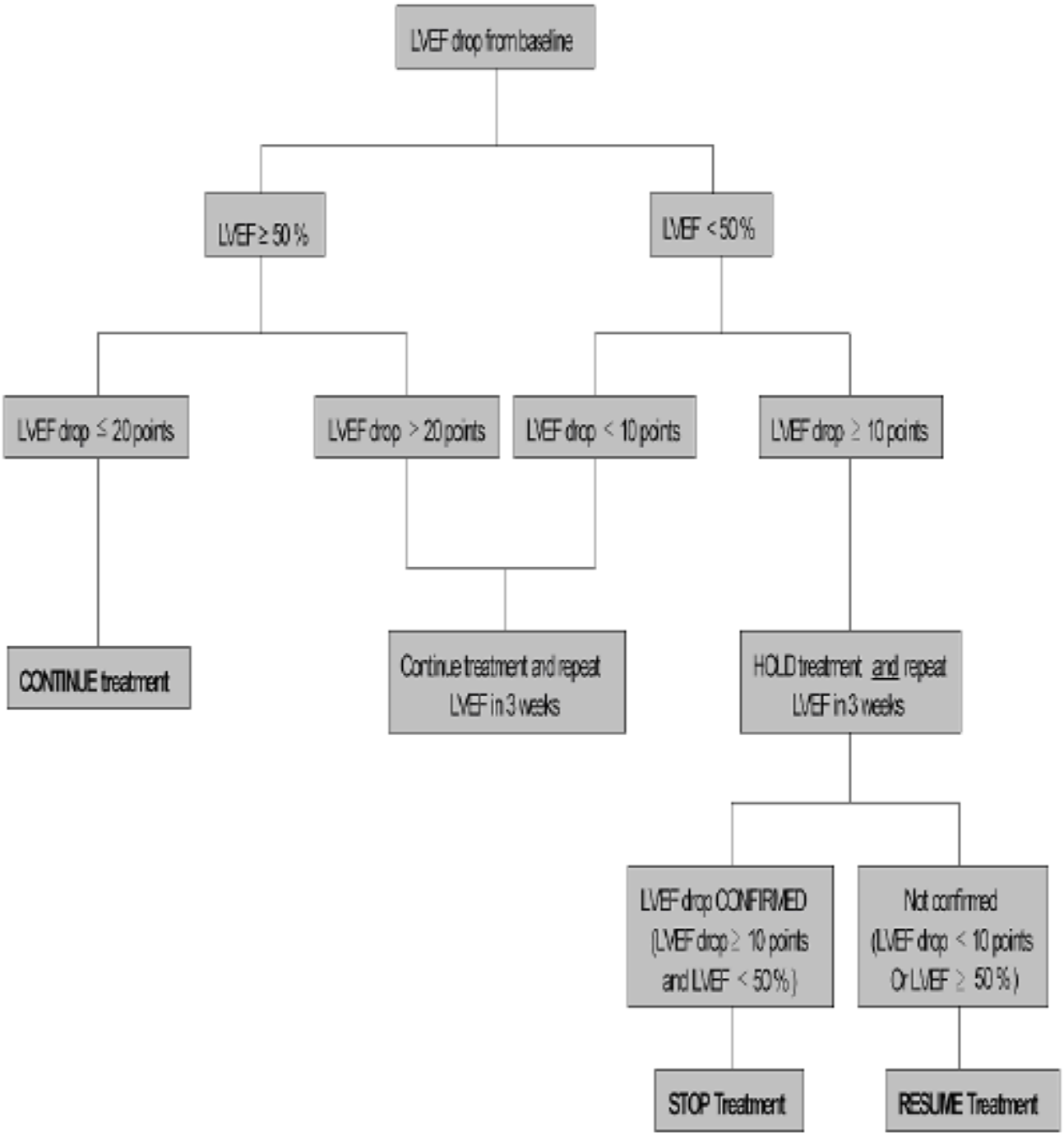
Delay the docetaxel where a NCI-CTC grade 3 cutaneous toxicity is present on day one of the cycle until it resolves to NCI-CTC grade 1 or below. The subsequent doses of docetaxel should be reduced to from 75mg/m^2 to 60mg/m^2. If it occurs with a dose of 60mg/m2 or if there is no recovery after two weeks, docetaxel treatment should be stopped. Where a NCI-CTC grade 3 cutaneous toxicity occurs between cycles with recovery by day one then reduce the docetaxel dose as described. Docetaxel should be stopped in response to a NCI-CTC grade 4 cutaneous toxicity.

Trastuzumab

The LVEF should be fifty or above before starting cycle one of trastuzumab.

Subsequent Echocardiograms

The flow chart below describes the process to be followed if there is an **asymptomatic** decline in LVEF during trastuzumab treatment.



In general patients who develop **symptomatic** cardiac dysfunction should have trastuzumab discontinued, be commenced on ACE inhibitor therapy and be referred to a cardiologist. Further treatment should be discussed with the relevant oncology consultant.

Regimen

The starting dose of carboplatin AUC6 is used with calculated GFR. AUC5 may be considered with EDTA clearance, seek advice from the appropriate consultant before prescribing. The recommended maximum dose when using a calculated creatinine clearance at AUC6 is 900mg. If you have an obese patient or an individual with a calculated creatinine clearance above 125ml/min please seek advice from the relevant consultant.

It should be noted that the dose of carboplatin may need to be altered if there is a change (improvement or reduction) in renal function of more than 10% from the previous cycle.

Docetaxel is highly myelosuppressive and in those with poor bone marrow reserves (for example due to extensive prior treatment, bone metastasis or extensive skeletal radiation) consider a starting dose of 55mg/m² with a view to increase to 75mg/m² if well tolerated.

21 day cycle for 6 cycles then trastuzumab alone for a further 12 cycles (18 cycles of trastuzumab in total)

Cycle 1

Drug	Dose	Days	Administration
Carboplatin	AUC 6 (max dose)	2	Intravenous infusion in 500ml glucose 5% over 60 minutes
Docetaxel	75mg/m^2	2	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
Trastuzumab	8mg/kg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes

Cycle 2, 3, 4, 5, 6

Drug	Dose	Days	Administration
Carboplatin	AUC 6 (max dose)	1	Intravenous infusion in 500ml glucose 5% over 60 minutes
Docetaxel	75mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
Trastuzumab	6mg/kg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

Cycle 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18

Drug	Dose	Days	Administration
Trastuzumab	6mg/kg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

Dose Information

- Carboplatin will be dose banded in accordance with the national dose bands (10mg/ml)
- The maximum dose of carboplatin for AUC 6 is 900mg. This will be set as 890mg in ARIA to comply with the national bands
- Docetaxel will be dose banded in accordance with the national dose bands
- Docetaxel induced fluid retention can lead to weight gain. This is not a reason to alter the doses
- Trastuzumab will be dose banded in accordance with national dose bands (21mg/ml)
- If the patient misses a dose of trastuzumab by fourteen days or less, then the usual maintenance dose of 6mg/kg should be given as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should be given according to the previous schedule
- If the patient misses a dose of trastuzumab by more than fourteen days, a re-loading dose of 8mg/kg should be given over 90 minutes. Subsequent maintenance doses should then be given every 21 days from that point

Administration Information

Hypersensitivity reactions tend to occur with the first or second infusion of docetaxel. The docetaxel infusion should not be interrupted for minor symptoms such as flushing or localised rashes. Immediately discontinue the infusion for severe reactions which include profound hypotension, bronchospasm and generalised erythema.

- Docetaxel doses of more than 200mg should be diluted in 500ml sodium chloride 0.9% (maximum concentration 0.74mg/ml)
- Trastuzumab is associated with hypersensitivity reactions. Patients should be observed for six hours following the start of the first infusion of trastuzumab and for two hours following the start of subsequent infusions. If the patient has tolerated the first two infusions with no infusion related effects consideration can be given to reducing this observation period further

Extravasation

- Carboplatin - irritant

- Docetaxel – exfoliant
- Trastuzumab – neutral

Additional Therapy

- Antiemetics

  15-30 minutes before chemotherapy

  - ondansetron 8mg oral or intravenous

  As take home medication

  - metoclopramide 10mg three times a day when required oral

- To prevent fluid retention and hypersensitivity reactions prescribe dexamethasone 8mg twice a day oral for three days starting 24 hours before the docetaxel administration. On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg once only dose intravenous bolus.

- For treatment of trastuzumab infusion reactions 'once only when required' doses of the following should be prescribed;

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous
  - paracetamol 1000mg oral

- Growth factors according to local policy

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

References
1. Valero V, Forbes J, Pegram MD et al. Multicentre phase III randomised trial comparing docetaxel and trastuzumab with docetaxel, carboplatin and trastuzumab as first line chemotherapy for patients with HER2 positive gene amplified metastatic breast cancer (BCIRG007 study); two highly active therapeutic regimens. J Clin Oncol 2011; 29 (2): 149-156.

REGIMEN SUMMARY

Carboplatin (AUC6)-Docetaxel-Trastuzumab (TCH)

Cycle 1

Day One

1. Dexamethasone 8mg twice a day oral*
   Administration Instructions
   Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat 15-30 minutes before chemotherapy.

2. Trastuzumab 8mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes

3. Chlorphenamine 10mg intravenous when required for infusion related reactions

4. Hydrocortisone 100mg intravenous when required for infusion related reactions

5. Paracetamol 1000mg oral when required for infusion related reactions
   Administration Instructions
   Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

Day Two

6. Dexamethasone 8mg twice a day oral (from TTO)*
   Administration Instructions
   Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat 15-30 minutes before chemotherapy.

7. Ondansetron 8mg oral or intravenous
   Administration Instructions
   Administer 15-30 minutes prior to SACT. This may be given as 8mg intravenous if required

8. Docetaxel 75mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes

9. Carboplatin AUC6 intravenous infusion in 500ml glucose 5% over 60 minutes
   Administration Instructions
   This recommended maximum dose is 900mg based on a creatinine clearance of 125ml/min. This will be set at 890mg in ARIA to comply with national dose bands

Take Home Medicines (given on day 1)

10. Dexamethasone 8mg twice a day oral for 3 days starting the day before the docetaxel infusion

11. Metoclopramide 10mg three times a day when required oral
    Administration Instructions
    Please supply 28x10mg tablets or nearest equivalent pack size

Cycles 2, 3, 4, 5

Day One

12. Dexamethasone 8mg twice a day oral
    Administration Instructions
    Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat 15-30 minutes before chemotherapy.

13. Trastuzumab 6mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

14. Ondansetron 8mg oral or intravenous
    Administration Instructions
    Administer 15-30 minutes prior to SACT. This may be given as 8mg intravenous if required

15. Docetaxel 75mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes

16. Carboplatin AUC6 intravenous infusion in 500ml glucose 5% over 60 minutes
    Administration Instructions
    This recommended maximum dose is 900mg based on a creatinine clearance of 125ml/min. This will be set at 890mg in ARIA to comply with national dose bands

17. Chlorphenamine 10mg intravenous when required for infusion related reactions

18. Hydrocortisone 100mg intravenous when required for infusion related reactions

19. Paracetamol 1000mg oral when required for infusion related reactions
    Administration Instructions
    Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

Take Home Medicines

20. Dexamethasone 8mg twice a day oral for 3 days starting the day before the docetaxel infusion

21. Metoclopramide 10mg three times a day when required oral
    Administration Instructions
    Please supply 28x10mg tablets or nearest equivalent pack size

Cycle 6

Day One

22. Dexamethasone 8mg twice a day oral
    Administration Instructions
    Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat 15-30 minutes before chemotherapy.

23. Trastuzumab 6mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

24. Ondansetron 8mg oral or intravenous
    Administration Instructions
    Administer 15-30 minutes prior to SACT. This may be given as 8mg intravenous if required

25. Docetaxel 75mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes

26. Carboplatin AUC6 intravenous infusion in 500ml glucose 5% over 60 minutes
Administration Instructions
This recommended maximum dose is 900mg based on a creatinine clearance of 125ml/min. This will be set at 890mg in ARIA to comply with national dose bands

27. Chlorphenamine 10mg intravenous when required for infusion related reactions

28. Hydrocortisone 100mg intravenous when required for infusion related reactions

29. Paracetamol 1000mg oral when required for infusion related reactions
Administration Instructions
Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

Take Home Medicines

30. Metoclopramide 10mg three times a day when required oral
Administration Instructions
Please supply 28x10mg tablets or nearest equivalent pack size

Cycle 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18

Day One

31. Trastuzumab 6mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

32. Chlorphenamine 10mg intravenous when required for infusion related reactions

33. Hydrocortisone 100mg intravenous when required for infusion related reactions

34. Paracetamol 1000mg oral when required for infusion related reactions
Administration Instructions
Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

*Cycle one dexamethasone must be prescribed in advance of the chemotherapy. In Aria Planner the dexamethasone 8mg twice daily will appear on days 1, 2, 3 of treatment. This is the supply for the next cycle. The administration instructions reflect this. On the last cycle no dexamethasone will appear for prescribing.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.3	July 2024	Trastuzumab updated with national dose banding	Alexandra Pritchard Pharmacist	Nanda Basker Pharmacist
1.2	Aug 2022	Carboplatin dose bands changed Docetaxel dose bands changed Coding removed Administration instructions added to summary	Dr Debbie Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	August 2014	Header changed Dose modification tabulated Hepatic impairment updated Carboplatin paragraph amended under regimen Metoclopramide dose changed to 10mg Bolus removed from intravenous bolus throughout text OPCS codes updated Disclaimer added	Donna Kimber Pharmacy Technician	Dr Debbie Wright Pharmacist
1	Jan 2013	None	Dr Debbie Wright Pharmacist	Dr Jenny Marshall Consultant Clinical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospitals NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.