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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>Neuropathy, nephrotoxicity, ototoxicity, thrombocytopenia</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Hypersensitivity, fluid retention, neuropathy, joint pains, nail changes, fatigue, alopecia, neutropenia</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Cardiotoxicity, acute respiratory distress syndrome, infusion related effects</td>
</tr>
</tbody>
</table>

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;

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Eligible Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>equal to or more than 1x10⁹/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>equal to or more than 100x10⁹/L</td>
</tr>
</tbody>
</table>

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 x10⁹/L or platelets less than 50 x10⁹/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>
<thead>
<tr>
<th>Drug</th>
<th>Bilirubin (µmol/L)</th>
<th>AST/ALT (units)</th>
<th>Alk Phos (units)</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>No dose adjustment needed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>N/A</td>
<td>1.5xULN or greater</td>
<td>2.5xULN or greater</td>
<td>Consider 75%</td>
</tr>
<tr>
<td></td>
<td>Greater than ULN</td>
<td>and</td>
<td>and</td>
<td>Not Recommended</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>No dose adjustment needed</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Renal Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>20ml/min or less</td>
<td>Contra-indicated</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>No dose adjustment necessary</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>No dose adjustment necessary</td>
<td></td>
</tr>
</tbody>
</table>

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/m² to 60mg/m². If the NCI-CTC grade 3 neuropathy occurred at doses lower than 75mg/m² 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/m². Symptomatic treatment with hyromellose 0.3% eye drops four times a day may help. However, if the ocular irritation continues reduce the docetaxel dose to 60mg/m² 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/m² to 60mg/m². 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>AUC 6 (max dose)</td>
<td>2</td>
<td>Intravenous infusion in 500ml glucose 5% over 60 minutes</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>75mg/m²</td>
<td>2</td>
<td>Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>8mg/kg</td>
<td>1</td>
<td>Intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes</td>
</tr>
</tbody>
</table>

Cycle 2, 3, 4, 5, 6

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
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<tbody>
<tr>
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<td>AUC 6 (max dose)</td>
<td>1</td>
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</tr>
<tr>
<td>Docetaxel</td>
<td>75mg/m²</td>
<td>1</td>
<td>Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>6mg/kg</td>
<td>1</td>
<td>Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes</td>
</tr>
</tbody>
</table>
Cycle 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>6mg/kg</td>
<td>1</td>
<td>Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes</td>
</tr>
</tbody>
</table>

**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 rounded to the nearest 50mg (up if halfway)
- 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 H₂ antagonist may be considered in patients considered at high risk of GI ulceration or bleed

References
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.
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.