PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Docetaxel, Carboplatin, Trastuzumab (T Carbo H) Breast Cancer Adjuvant Protocol

PROTOCOL REF: MPHATCHBR
(Version No. 1.1)

Approved for use in:

Adjuvant treatment in HER2 positive breast cancer. For PS 0 to 1 and/or moderate/high risk patients in whom an anthracycline is contraindicated.

Dosage:

Drug	Dosage	Route	Frequency
Docetaxel	**75mg/m^2**	Intravenous Infusion	Every 21 days For cycles 1 to 6 ONLY
Carboplatin	**AUC 5 or 6 (Maximum dose 890mg)**		
Trastuzumab	**600mg**	Subcutaneous	Every 21 days For cycles 1 to18

*Use area under the curve (AUC) 5 for GFR calculations utilising Wright formula and AUC 6 when calculating Creatinine Clearance (CrCl) using Cockroft and Gault formula. The formula used at the start of treatment will then need to be used throughout the whole carboplatin treatment course. If estimated GFR is used the **Wright formula and AUC 5** must be used for creatinine clearance.

Meditech calculates creatinine clearance using the Wright formula (AUC5). There is the option to select carboplatin within the order set where Cockroft and Gault equation can be used manually to enter a calculated dose of carboplatin using AUC6, as undertaken in the clinical

trial for this regimen. Applications for calculating creatinine using both formulas are available on the Remote Citrix Web Portal.

In both cases (whether using AUC 5 or 6) Maximum dose of carboplatin is 890mg.

Calvert formula for Carboplatin dosage-:

Carboplatin dose in mg = AUC x (GFR or CrCl + 25)

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Dexamethasone 8mg orally twice a day for 3 days, commencing 1 day **prior to docetaxel administration** to prevent hypersensitivity reactions.

Ondansetron 16mg orally or 8mg IV day 1.

Metoclopramide 10mg orally up to three times a day when required when required for nausea and vomiting (maximum 5 consecutive days)

Filgrastim subcutaneous injection daily for 7 days starting on day 3, dose as follows:

- Weight < 70kg- Filgrastim 300 micrograms daily SC.
- Weight ≥ 70kg- Filgrastim 480 micrograms daily SC.

Extravasation risk:

Docetaxel – exfoliant

Carboplatin – irritant

Trastuzumab – neutral

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

<table>
<tr><td rowspan="3">Renal</td><td>Carboplatin</td><td>Patients with creatinine clearance values of less than 60 mL/min are at greater risk to develop myelosuppression.

The optimal use of Carboplatin in patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both haematological nadirs and renal function.

Carboplatin is contraindicated if GFR or CrCl ≤ 20 ml/min. Do not give carboplatin and discuss with clinical team.</td></tr>
<tr><td>Docetaxel</td><td rowspan="2">All grades including patients on HDx - no dose adjustment required.</td></tr>
<tr><td>Trastuzumab</td></tr>
<tr><td rowspan="3">Hepatic</td><td>Docetaxel</td><td><table>
<tr><th></th><th>Dose</th></tr>
<tr><td>AST and/or ALT > 1.5 to 5 x upper limit normal (ULN) concomitant with ALP > 2.5 to 5.0 x ULN and normal bilirubin</td><td>75%</td></tr>
<tr><td>AST or ALT >1.5 to 5 x ULN concomitant with ALP ≤ 2.5 to 6 x ULN and/or bilirubin ≤ 1to 1.5 x ULN</td><td>50%</td></tr>
<tr><td>Bilirubin > 1.5 x ULN
or
AST/ALT > 10 x ULN
or
ALP > 6 x ULN</td><td>Not recommended</td></tr>
</table></td></tr>
<tr><td>Carboplatin</td><td rowspan="2">No need for dose adjustment is required.</td></tr>
<tr><td>trastuzumab</td></tr>
</table>

Interactions:

Please refer to the SmPC for full list of interactions.

Carboplatin	Concomitant use contraindicated- **Yellow fever vaccine** Use not recommended- Live attenuated vaccines, phenytoin and fosphenytoin Use with caution in combination with immunosuppressants (tacrolimus, sirolimus and ciclosporin), nephrotoxic drugs (**amino glycosides, vancomycin, capreomycin and diuretics**. Concomitant use with loop diuretics (furosemide,indapamide,bumetanide): increased the risk of nephrotoxicity and ototoxicity.
Docetaxel	Avoid concomitant use of a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole).
Trastuzumab	No formal drug interaction studies have been performed. Clinically significant interactions between trastuzumab and the concomitant medicinal products used in clinical trials have not been observed.

Treatment schedule:

Cycles 1 to 6

Day	Drug	Dose	Route	Diluent and rate
1	Ondansetron	16mg	PO	30 minutes before chemotherapy
	Dexamethasone	8mg BD	PO	Orally for 3 days, commencing 24 hours before docetaxel*.
	Docetaxel	**75mg/m^2**	**IV**	**IV infusion over 60 minutes in 250mL sodium chloride 0.9%**
	Trastuzumab	**600mg**	**SC**	Over 5 minutes
	Carboplatin	**AUC 5 or 6**	**IV**	**500mL glucose 5% over 60 minutes**

Repeated every 21 days

*If oral dexamethasone has not been taken then an intravenous dose of 8mg can be administered on the day of treatment, in addition to the oral dose of 8mg

As with all taxane and platinum based chemotherapy, patients may experience allergic reaction during administration. Please refer to the CCC Hypersensitivity; Management Prevention Policy.

For severe reactions, discuss with Consultant before continuing with treatment. It should be strongly noted that patients who have severe reactions should not be re-challenged.

Cycles 7 to 18

Day	Drug	Dose	Route	Diluent and rate
1	**Trastuzumab**	**600mg**	**SC**	**Over 5 minutes**

Repeated every 21 days

Main toxicities:

Haematological	Neutropenia, thrombocytopenia and anaemia.
Gastrointestinal	Nausea, vomiting, stomatitis, diarrhoea, mucositis.
Cardiotoxicity	Trastuzumab - decreases in LVEF have been reported with medicinal products that block HER2 activity, including Trastuzumab; see cardiotoxicity dose modification section below
Respiratory	Acute respiratory distress syndrome, pneumonitis
Dermatological	Alopecia, normally reversible, although can be permanent following docetaxel. Docetaxel: Brittle, chipped and ridged nails
Urological	Carboplatin is nephrotoxic.
Ototoxicity	Common when carboplatin used in high doses.
Ocular	Watery eyes, gritty and irritated. Risk of cortical blindness with carboplatin; renal impairment is thought to increase this risk.
Hypersensitivity reactions	Reactions may occur within a few minutes of starting docetaxel, facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised rash with or without pruritus do not require interruption

	of therapy. Severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate treatment. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel. Trastuzumab: Infusion reactions, allergic-like reactions and hypersensitivity can occur. The majority of these events occur during or within 2.5 hours of the start of the first infusion and are less likely with subcutaneous injection
General disorders	Carboplatin: Decreases in serum electrolytes (sodium, magnesium, potassium and calcium) Hyperuricaemia: Serum levels of uric acid can be decreased by allopurinol.
Nervous system	Docetaxel: peripheral neuropathy is very common Carboplatin: Can cause paraesthesia and decreased deep tendon reflexes
Musculoskeletal	Arthralgia, myalgia common with docetaxel
Infertility	Amenorrhea, risk of premature menopause However ensure appropriate contraceptive advice is given

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Ongoing
Informed Consent	x							
Clinical Assessment	x		x		x		x	Alternate cycles for cycles 1 to 6 then 12 weekly
SACT Assessment (to include PS and toxicities)	x	x	x	x	x	x	x	Every cycle
FBC	x	x	x	x	x	x	x	Every cycle for Cycles 1 to 6 (while on chemotherapy component)
U&E & LFTs & Magnesium	x	x	x	x	x	x	x	
Calculate GFR or CrCl and check carboplatin dose using the carboplatin calculator*	x	x	x	x	x	x	x	
ECG								If clinically indicated
ECHO	x				x			3 to 4 monthly whilst on trastuzumab

Full observations		x	x	x	x	x	x	Every cycle
Weight recorded	x	x	x	x	x	x	x	Every cycle
Height	x							

* Please refer to:

- 'Dosage' section for full details on carboplatin dosing.
- 'Carboplatin Dosing Calculator' SOP outlining process for checking carboplatin dose ahead of each cycle of treatment.

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycles 1 to 6

Proceed on day 1 if-

Plt ≥ 100 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Delay 1 week on day 1 if-

Plt ≤ 99 x 10^9/L	ANC ≤ 0.9 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Cycle 7 onwards (Trastuzumab ONLY)

No blood tests required.

Non- Haematological toxicity:

Peripheral Neuropathy

NCI-CTC grade 2 peripheral neuropathy: withhold taxane until neuropathy recovers to grade 1 then dose reduce by 20%

If NCI-CTC grade 3 (or persistent grade 2) peripheral neuropathy occurs, discontinue taxane.

Pulmonary Impairment:

Trastuzumab-Pulmonary events have been reported with the use of trastuzumab.

These events have occasionally been fatal.

Caution should be exercised for pneumonitis.

Hypersensitivity

Taxanes- If hypersensitivity reactions occur; minor symptoms, such as flushing or localised rash with or without pruritus, do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of taxane and appropriate treatment. Patients who have developed severe hypersensitivity reactions should not be re-challenged.

Should an infusion reaction occur the infusion should be discontinued. The symptoms should be managed using paracetamol, with addition of chlorphenamine and hydrocortisone if anaphylaxis suspected. Please refer to the CCC Hypersensitivity; Management Prevention Policy.

Patients should be monitored until resolution of all observed symptoms. Patients experiencing dyspnoea at rest may be at increased risk of a fatal infusion reaction; these patients should not be treated with trastuzumab.

Cardiotoxicity

Management of Trastuzumab and Pertuzumab-Induced Cardiotoxicity (refer to NCRI recommendations 2009 outlined below)

- Sharp falls in LVEF (10 points or to <50%) during cytotoxic chemotherapy may indicate increased susceptibility to cardiac dysfunction on trastuzumab Prophylactic ACE inhibitor therapy may be considered for such patients.
- Assessment at the end of treatment is recommended for patients requiring cardiovascular intervention during treatment.
- Additional testing is required in patients who have LV systolic dysfunction.

- 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 a level above the LLN.
- If the LVEF falls to below the LLN but > 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 the LLN, trastuzumab may be continued. Intervention with an ACE inhibitor is recommended in an attempt to reduce the risk of further LVEF decline of symptomatic CHF.
- LVEF Monitoring should be repeated after 6–8 weeks.

NCRI recommendations for cardiac monitoring
Ref: British Journal of Cancer 2009 100:684-692

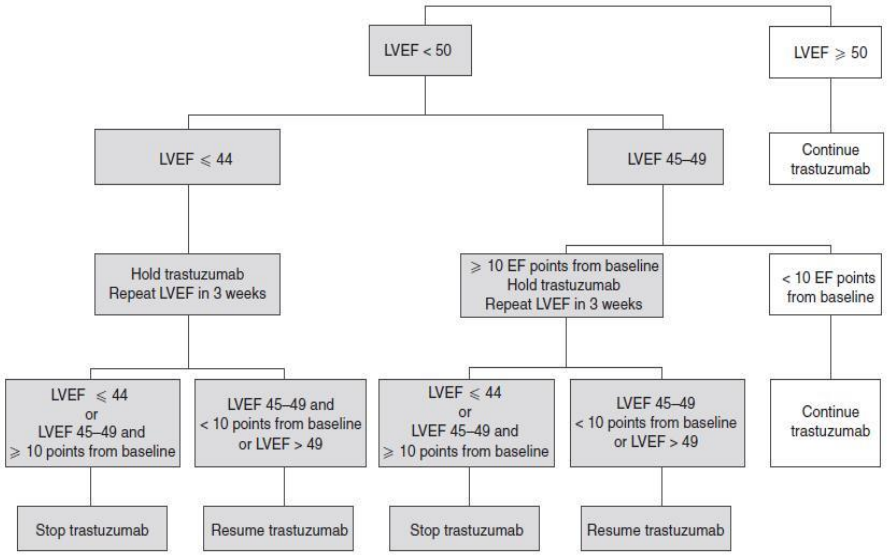

Figure 1 Current recommendations for cardiac monitoring in trastuzumab-treated patients (reproduced from Suter *et al*, 2007; online Appendix only). Reproduced with permission of the American Society of Clinical Oncology, from Suter *et al*, 2007.

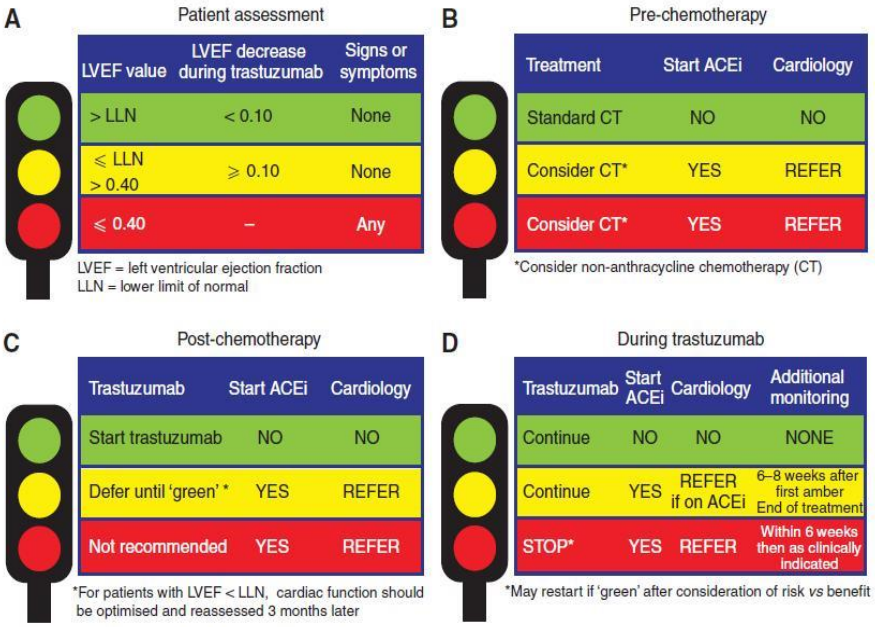

Figure 2 Traffic light system to prevent, monitor, and manage cardiac events in patients undergoing cytotoxic chemotherapy. (**A**) Patient assessment during trastuzumab therapy; (**B**–**D**) indications for ACEi therapy and referral to a cardiologist before (**B**) and after (**C**) chemotherapy, and (**D**) during trastuzumab therapy, when additional cardiac assessments may also be required. ACEi = angiotensin-converting enzyme inhibitor.

References:

- Slamon, Dennis, et al (2011). "Adjuvant trastuzumab in HER2-positive breast cancer." *New England journal of medicine*.14:1273-1283.
- SmPC for Carboplatin 10 mg/ml Intravenous Infusion, Hospira – accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated 16th June 2020).
- SmPC for 600 mg solution for injection in vial, Roche- accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated 28th September 2021).
- SmPC for Docetaxel Accord 20 mg/1 ml concentrate for solution for infusion- accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated 16th October 2020).
- Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20: e201–08.

Circulation/Dissemination

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Date document posted on the Intranet	N/A

Version History

		Author name and designation	Summary of main changes
		Helen Flint **Consultant Pharmacist**	New Protocol Regimen V1.0

			Hala Ghoz **Lead Protocols Pharmacist**	Routine Protocol Update V1.1