Systemic Anti Cancer Treatment Protocol

T Carbo H
Docetaxel, Carboplatin, Trastuzumab, Adjuvant Protocol

PROTOCOL REF: MPHATCHBR
(Version No: 1.0)

Approved for use in:

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

Dosage:

Drug	Dosage	Route	Frequency
Docetaxel	**75mg/m^2**	IV	Every 21 days
Carboplatin	**AUC5***	IV	
Trastuzumab	**600mg**	s/c	

Every 21 days for 6 cycles, continue with trastuzumab maintenance to 18 cycles in total.

***Notes: Meditech uses Wright formula to calculate estimated creatinine clearance**
For automated dose calculation this will be at AUC5

Calvert formula for Carboplatin dosage:

Carboplatin dose in mg = AUC x (creatinine clearance + 25)

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.

If this option is selected a **prescription note must be written at time of prescribing** detailing the parameters used to calculate the dose. Pharmacy will then adjust to the national dose bands. Without a note the prescription will not be processed.

Maximum dose of carboplatin via either method = 890mg

Supportive Treatments:

Dexamethasone 8mg BD orally for 3 days, commencing 24 hours before docetaxel.
Ondansetron 16mg PO or 8mg IV day 1.
Domperidone 10mg tablets orally three times a day when required

Filgrastim subcutaneous injection daily for 7 days from day 3 (dose of 300 micrograms for patients below 70kg, and 480 micrograms for those 70kg and above)

Extravasation Risk:

Carboplatin – irritant
Trastuzumab – neutral
Docetaxel - vesicant

Administration:

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**	**S/C**	Over 5 minutes
	Carboplatin	**AUC 5**	**IV**	**500mL glucose 5% over 60 minutes**

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

Cycles 7 to 18

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

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	Carboplatin: Paraesthesia and decreased deep tendon reflexes. Docetaxel: peripheral neuropathy is very common
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	Comments
Medical Assessment	X		X		X		X	Alternate cycles. Trastuzumab: every 12 weeks
Nursing Assessment	X	X	X	X	X	X	X	Every cycle
ECHO / ECG	X				X			12 weekly whilst on trastuzumab
FBC	X	X	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	X	X	Every cycle
Calculate CrCl	X	X	X	X	X	X	X	Every cycle
Informed Consent	X							
PS recorded	X	X	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Haematological Toxicity:

Proceed on day 1 if-

Plt ≥ 100 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Hepatic Impairment:

Docetaxel
If Bilirubin >22µmol/L +/or ALT/AST >3.5 times ULN with ALP > 6 times ULN, docetaxel should not be used unless strictly indicated.
Carboplatin
Minimal hepatic metabolism; no specific dosage adjustment guidelines are available.
Trastuzumab
No data is currently available

Renal impairment:

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.

In case of a glomerular filtration rate of ≤ 20 mL/min, carboplatin should not be administered at all.

There are no data available in patients with severely impaired renal function treated with docetaxel. Docetaxel has minimal renal excretion; dosage adjustments for renal impairment may not be needed.

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.

Peripheral Neuropathy

NCI-CTC grade 2 peripheral neuropathy – withhold chemotherapy until recovers to grade 1 then dose reduce docetaxel by 20%. If neuropathy persists consider dose reducing carboplatin at subsequent cycles

Myalgia/arthralgia

Often co-exist, usually grade 1 or 2. Manage with reassurance that the condition is self-limiting. NSAIDs may be considered but they may be ineffective.

Trastuzumab cardiotoxicity

Dose reductions are not indicated to manage toxicity

FBC is not required prior to treatment

See cardiac toxicity guidance on next page

- 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

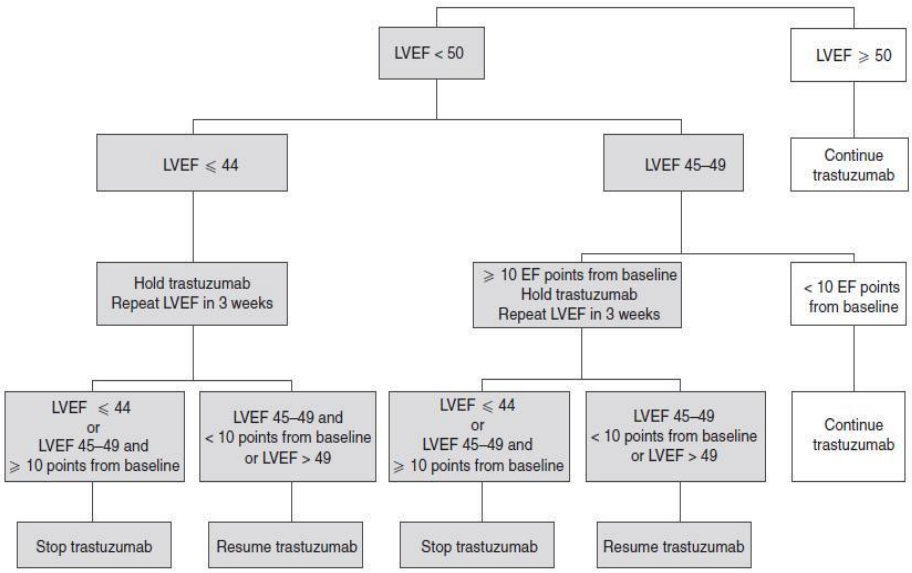

Figure 1 Current recommendations for cardiac monitoring in trastuzumab-treated patients (reproduced from Suter *et al*, 2007; online Appendix only). Reproduced with permission of the American Society of Clinical Oncology, from Suter *et al*, 2007.

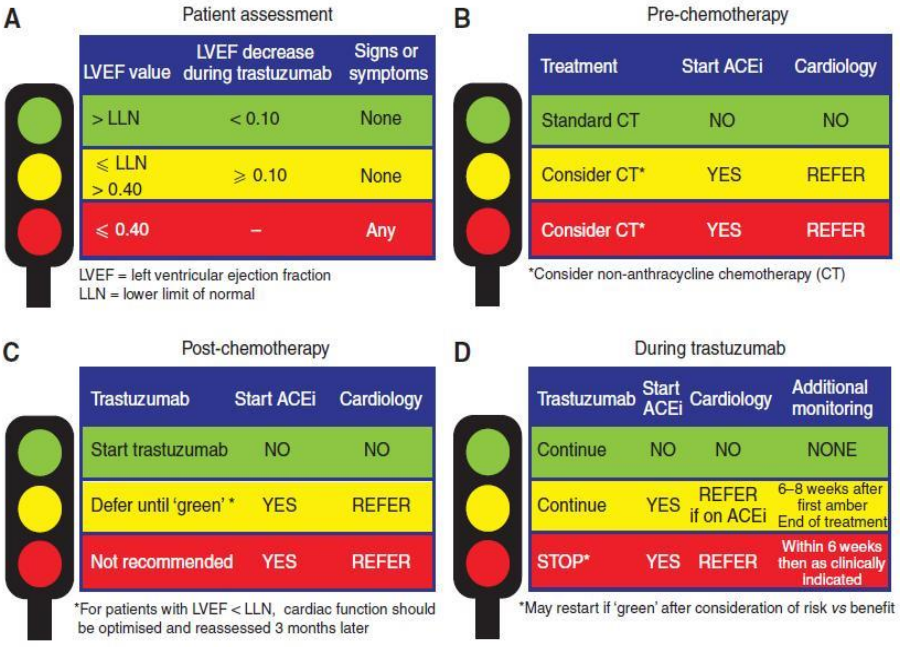

Figure 2 Traffic light system to prevent, monitor, and manage cardiac events in patients undergoing cytotoxic chemotherapy. (**A**) Patient assessment during trastuzumab therapy; (**B**–**D**) indications for ACEi therapy and referral to a cardiologist before (**B**) and after (**C**) chemotherapy, and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

References:

Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009 UCLH (Version 3 - updated January 2009)

Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH (Version 3 - updated January 2009)

Stockley's drug interactions. Ninth edition. Edited K. Baxter. Pharmaceutical press. London. 2010.

Cheshire And Merseyside Strategic Clinical Network Guidance for the Prevention and Management of Extravasation Injuries (Version 6.0 – January 2016). Available via CCC intranet.

Drug Information Handbook for Oncology, 7th Edition, Lexi Comp.

Creatinine Clearance

Wright Creatinine Clearance Formula

Male patients $\frac{(6580 - (38.8 \times \text{age})) \times \text{bsa}}{\text{creatinine}}$

Female patients $\frac{(6580 - (38.8 \times \text{age})) \times \text{bsa} \times 0.832}{\text{creatinine}}$

Cockroft and Gault formula

Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

NB Weight in kg

Creatinine in micromol/L