Systemic Anti Cancer Treatment Protocol

TCHP
Docetaxel, Carboplatin, Trastuzumab, Pertuzumab Neoadjuvant Protocol

PROTOCOL REF: MPHATCHP

(Version No: 1.0)

Approved for use in:

Neoadjuvant breast: The neoadjuvant treatment of HER2 positive locally advanced, inflammatory or early breast cancer at high risk of recurrence.

Dosage:

Drug	Dosage	Route	Frequency
Docetaxel	**75mg/m^2**	IV	Every 21 days
Carboplatin	**AUC 6**	IV	
Trastuzumab	**8mg/kg loading dose then 6mg/kg to cycle 6 Post operatively switch to subcutaneous route**	IV	
Pertuzumab	**840mg loading dose Then 420mg cycles 2 to 6.**	IV	

Note: meditech calculates creatinine clearance using the Wright formula and therefore creatinine clearance will need to be entered manually to use Cockroft and Gault formula

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:

Docetaxel – vesicant
Carboplatin – irritant
Trastuzumab – neutral
Pertuzumab – neutral

Administration:

Cycle 1

Day	Drug	Dose	Route	Diluent and rate
1	Ondansetron	16mg	PO	30 minutes before chemotherapy
	Pertuzumab	**840mg**	**IV**	**250mL sodium chloride 0.9% over 60 minutes**
	Trastuzumab	**8mg/kg**	**IV**	**250mL sodium chloride 0.9% over 90 minutes**
	Docetaxel	**75mg/m^2**	**IV**	**250mL 0.9% sodium chloride over 60 minutes**
	Carboplatin	**AUC 6**	**IV**	**500mL glucose 5% over 60 minutes**

Cycle 2 to 6

Day	Drug	Dose	Route	Diluent and rate
1	Ondansetron	16mg	PO	30 minutes before chemotherapy
	Pertuzumab	**420mg**	**IV**	**250mL sodium chloride 0.9% over 30 minutes**
	Trastuzumab	**6mg/kg**	**IV**	**250mL sodium chloride 0.9% over 60 minutes at cycle 2 then over 30 minutes if tolerated**
	Docetaxel	**75mg/m^2**	**IV**	**250mL 0.9% sodium chloride over 60 minutes**
	Carboplatin	**AUC 6**	**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

Cycle 7 to 18 (post surgical continuation of trastuzumab)

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

Main Toxicities:

TCH-P	
Haematological	Neutropenia, thrombocytopenia and anaemia.
Gastrointestinal	Nausea, vomiting, stomatitis, diarrhoea, mucositis.
Cardiotoxicity	Pertuzumab and Trastuzumab - decreases in LVEF have been reported with medicinal products that block HER2 activity, including Pertuzumab and Trastuzumab; see cardiotoxicity dose modification section below for details.
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 following the initiation of treatment with 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. However, 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. Patients should be monitored for hypersensitivity and infusion reactions with Pertuzumab for 60 minutes after the first dose, and for 30 minutes after subsequent doses.

	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. Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the patient 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.

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
Nursing Assessment	X	X	X	X	X	X	X	Every cycle
ECHO / ECG	X				X			12 weekly
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

Delay 1 week on day 1 if-

Plt ≤ 99 x 10^9/L	ANC ≤ 0.9 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. ALT +/or AST > 1.5 times ULN and ALP > 2.5 times ULN – give 75mg/m^2

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.

Pulmonary Impairment:

Trastuzumab:
Pulmonary events have been reported with the use of Trastuzumab. These events have occasionally been fatal.
Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events and should therefore not be treated with Trastuzumab.
Caution should be exercised for pneumonitis.

Cardiotoxicity: Pertuzumab and Trastuzumab;

NCRI recommendations for cardiac monitoring

Ref: British Journal of Cancer 2009 100:684-692

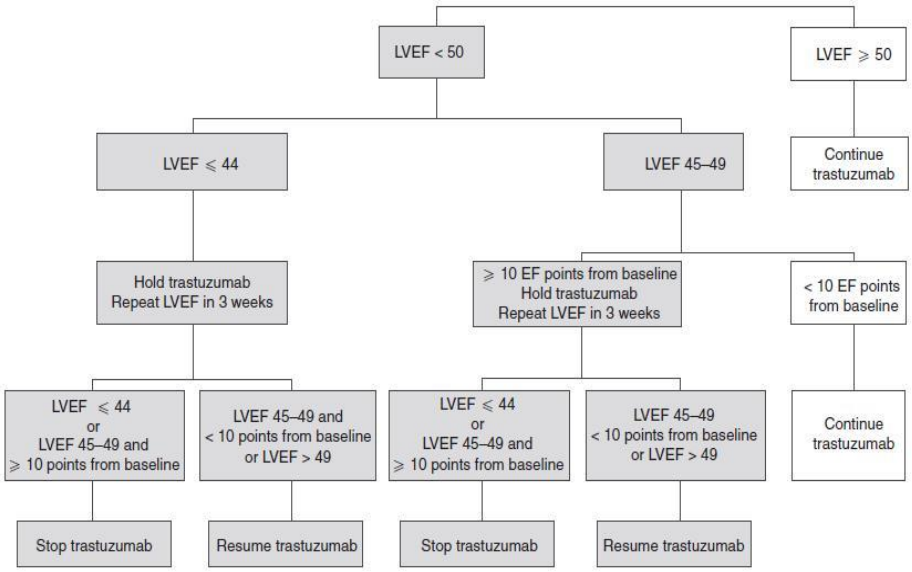

Figure 1 Current recommendations for cardiac monitoring in trastuzumab-treated patients (reproduced from Suter *et al*, 2007; online Appendix only). Reproduced with permission of the American Society of Clinical Oncology, from Suter *et al*, 2007.

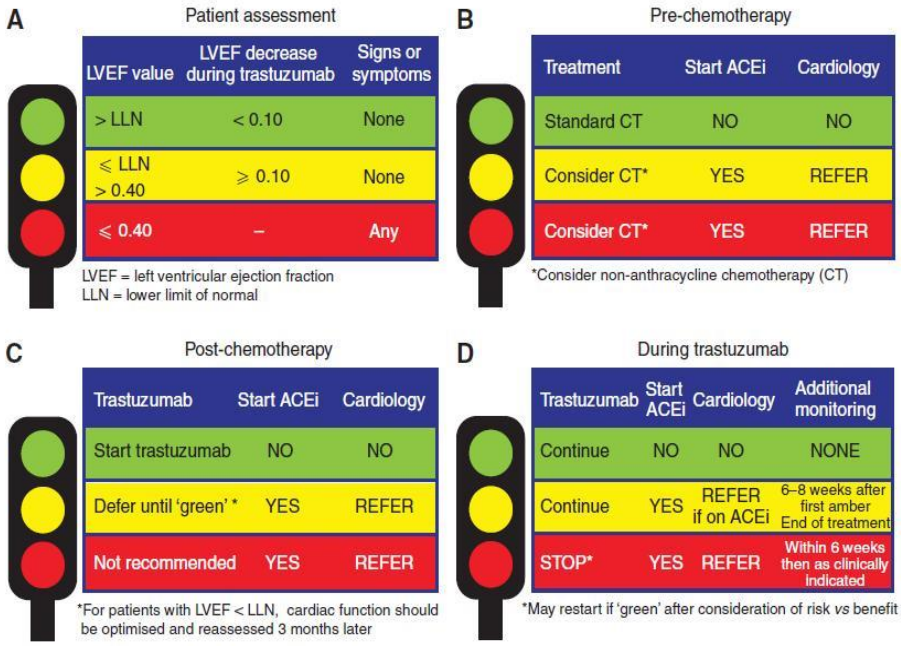

Figure 2 Traffic light system to prevent, monitor, and manage cardiac events in patients undergoing cytotoxic chemotherapy. (**A**) Patient assessment during trastuzumab therapy; (**B**–**D**) indications for ACEi therapy and referral to a cardiologist before (**B**) and after (**C**) chemotherapy, and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

Pertuzumab and trastuzumab should be withheld for at least 3 weeks for any of the following:

- signs and symptoms suggestive of congestive heart failure
- a drop in left ventricular ejection fraction (LVEF) to less than 45%
- LVEF of 45% to 49% associated with a fall of ≥ 10 points below pre-treatment values.

Perjeta and trastuzumab may be resumed if the LVEF has recovered to > 45% or 40-45% associated with < 10% points below pre-treatment value.

If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, discontinuation of Pertuzumab and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

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.

SPC for Pertuzumab (Perjeta 420mg Concentrate for solution for Infusion, Roche) – accessed via electronic medicines compendium at www.medicines.org.uk

SPC for Trastuzumab (Herceptin 150mg powder for concentrate for solution for infusion, Roche) - accessed via electronic medicines compendium at www.medicines.org.uk

TRYPHAENA trial
Annals of Oncology 24: 2278–2284, 2013

NEOSPHERE trial
Lancet Oncol 2012; 13: 25–32