Systemic Anti Cancer Treatment Protocol

EC-D with HP
Epirubicin, Cyclophosphamide, Followed by Docetaxel, Trastuzumab, Pertuzumab Neoadjuvant Protocol

PROTOCOL REF: MPHAECDHPBR
(Version No: 1.0)

Approved for use in:

Neoadjuvant breast cancer: The neoadjuvant treatment of HER2 positive T2 to T4 and/or histologically or cytologically proven node positive early breast cancer

Blueteq registration required

Dosage:

Drug	Dosage	Route	Frequency
Epirubicin	90mg/m²	IV	Cycles 1 to 3 Day 1 only of a 21 day cycle
Cyclophosphamide	600mg/m²	IV	
Followed by			
Docetaxel	Initially 75mg/m^2 Can increase to 100mg/m^2 at cycle 5 at consultants discretion.	IV	Cycles 4 to 7 Day 1 only of a 21 day cycle
Trastuzumab	8mg/kg loading dose cycle 4. Then 6mg/kg cycle 5, 6 and 7. To continue for 18 doses in total; should switch to subcutaneous post surgery	IV	Cycles 4 to 7 Day 1 only of a 21 day cycle
Pertuzumab	840mg loading dose cycle 4. Then 420mg cycles 5, 6 and 7.	IV	Cycle 4 to 7 Day 1 only of a 21 day cycle

Supportive Treatments:

Ondansetron 8mg orally twice a day for three days

Domperidone 10mg tablets, three times a day as 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)

Additional item EC – cycles one to three

Dexamethasone 4mg orally twice a day for three days

Additional item Docetaxel – cycles four to seven

Premedication of dexamethasone 8 mg twice daily for 3 days starting 1 day prior to docetaxel administration

Docetaxel can be administered as the first part of the regimen i.e. cycles 1 to 4, followed by EC as cycles 5 to 7 if surgery can be scheduled following cycle 4 (as NEOSPHERE trial protocol)

Extravasation risk:

Epirubicin is a vesicant. Erythematous streaking along the vein proximal to the site of injection has been reported, and must be differentiated from an extravasation event. This reaction usually subsides within 30 minutes.

Cyclophosphamide- neutral

Pertuzumab- non-vesicant

Trastuzumab- non-vesicant

Docetaxel - exfoliant

Administration:

EC Cycles 1-3

Day	Drug	Dose	Route	Diluent and rate
1	**Ondansetron**	**24mg**	**PO**	30mins before chemotherapy
	Dexamethasone	**12mg**	**PO**	30mins before chemotherapy
	Epirubicin	**90mg/m^2**	**IV**	IV bolus over 10 to 15 minutes Concurrent administration, doxorubicin at 400mL/hr and sodium chloride 0.9% at 100mL/hr
	Cyclophosphamide	**600mg/m^2**	**IV**	IV bolus over 30 minutes

Repeat every 21 days for 3 cycles – at cycle 3 ensure patient has dexamethasone for prior to docetaxel

- Nasal stuffiness can occur immediately with administration of cyclophosphamide, if uncomfortable for the patient the drug can be slowed down
- Encourage an oral fluid intake of 2 litres per day to promote urinary output & prevent chemical cystitis with cyclophosphamide.

Docetaxel, Trastuzumab, Pertuzumab Cycle 4

Day	Drug	Dose	Route	Diluent and rate
Premedication: Dexamethasone 8 mg twice daily for 3 days starting 1 day prior to docetaxel administration				
1	**Ondansetron**	**8mg**	**Oral**	30mins before chemotherapy
1	**Pertuzumab**	**840mg**	**IV**	**250mL sodium chloride 0.9% over 60 minutes**
1	**Trastuzumab**	**8mg/kg**	**IV**	**250mL sodium chloride 0.9% over 90 minutes**
1	**Docetaxel**	**75mg/m^2**	**IV**	**250mL sodium chloride 0.9% over 60 minutes**

Docetaxel, Trastuzumab, Pertuzumab Cycles 5, 6 and 7

Day	Drug	Dose	Route	Diluent and rate
Dexamethasone 8 mg twice daily for 3 days starting 1 day prior to docetaxel				
1	**Ondansetron**	**8mg**	**Oral**	30mins before chemotherapy
1	**Pertuzumab**	**420mg**	**IV**	**250mL sodium chloride 0.9% over 30 minutes**
1	**Trastuzumab**	**6mg/kg**	**IV**	**250mL sodium chloride 0.9% over 60 minutes at cycle 5 and then 30 minutes if well tolerated**
1	**Docetaxel**	**75mg/m^2 Can increase to 100mg/m^2 at this point if consultant deems fit.**	**IV**	**250mL sodium chloride 0.9% over 60 minutes**

Cycles 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

Post surgery – to complete 18 doses of trastuzumab (cycles 5 to 18)

To commence 3 weeks after final cycle of chemotherapy (cycle 5 of trastuzumab may be before surgery has taken place)

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
Cardiotoxicity	Epirubicin - sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Other cardiac events have been reported, included delayed toxicity. 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.
Respiratory	Acute respiratory distress syndrome, pneumonitis
Dermatological	Alopecia, small risk of permanent alopecia following docetaxel Docetaxel: Brittle, chipped and ridged nails.
Urological	Red colouration of urine for 1 to 2 days after administration following epribucin Urotoxicity can occur with short-term and long-term use of cyclophosphamide. Hemorrhagic cystitis, pyelitis, ureteritis, and haematuria. Mesna can be given if required.
Ocular	Watery eyes, gritty and irritated

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.
Nervous system	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	Comments
Medical Assessment	X		X		X		Alternate cycles. Then every 3 months whilst on trastuzumab
Nursing Assessment	X	X	X	X	X	X	Every cycle
ECHO	X			X			ECHO must be performed before trastuzumab commences. Then every 4 months whilst on trastuzumab
FBC	X		X	X	X	X	Every cycle
U&E & LFT	X		X	X	X	X	Every cycle
Informed Consent	X						
PS recorded	X	X	X	X	X	X	Every cycle
Toxicities documented			X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Haematological Toxicity:

Proceed with treatment if;

Neutrophils $\geq$ 1.0 **and** platelets $\geq$ 100 x 10^9/L

Defer by 7 days or until blood counts recovered if Neutrophils $\leq$ 1.0 **or** platelets $\leq$ 100 x 10^9/L

Second episode or severe neutropenic sepsis: Defer by 7 days or until blood counts recovered if Neutrophils $\leq$ 1.0 **or** platelets $\leq$ 100 x 10^9/L **and reduce** to 80% dose

For trastuzumab only cycles – no blood tests required

Hepatic impairment:

	Epirubicin	Cyclophosphamide
Bilirubin µmol/L	**Dose**	**Dose**
24 to 50	50%	100%
51 to 85	25%	75%
Above 85	Omit	Omit

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:

No dose adjustments required for moderate renal impairment.

Peripheral Neuropathy

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

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

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.

Trastuzumab Dose Modifications and Toxicities;

Hypersensitivity

Injection-related symptoms (mild to moderate in severity): fever, chills, headache, nausea, rash, arthralgia/myalgia (occur mainly with 1st intravenous dose) and anaphylaxis. These symptoms should be managed using paracetamol, with addition of chlorphenamine and hydrocortisone if anaphylaxis suspected.

Dose reductions are not indicated to manage toxicity

- Sharp falls in LVEF (10 points or to <50%) during cytotoxic chemotherapy may indicate increased susceptibility to cardiac dysfunction on trastuzumab/pertuzumab. 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/pertuzumab 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/pertuzumab 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.

Cardiotoxicity: Pertuzumab and Trastuzumab;

NCRI recommendations for cardiac monitoring

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

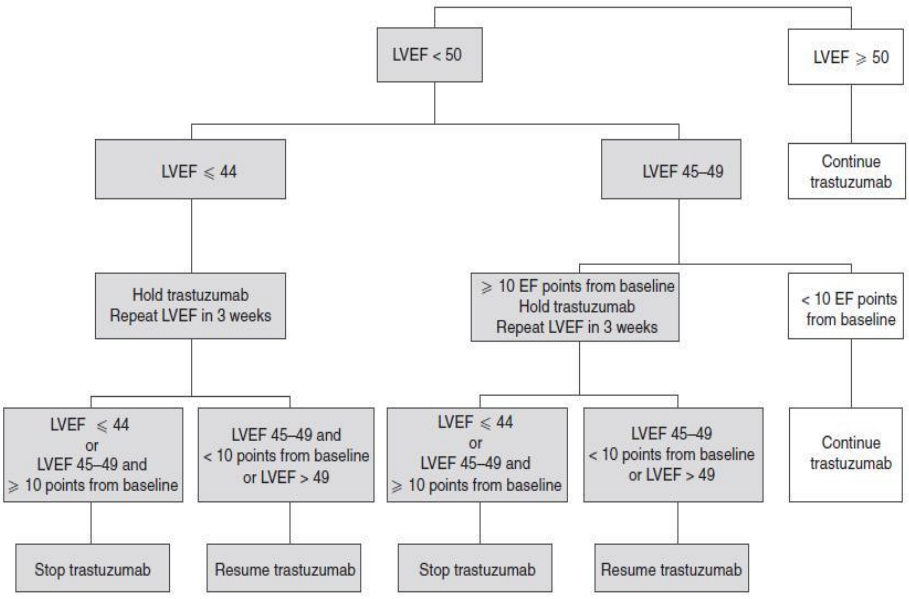

Figure 1 Current recommendations for cardiac monitoring in trastuzumab-treated patients (reproduced from Suter *et al*, 2007; online Appendix only). Reproduced with permission of the American Society of Clinical Oncology, from Suter *et al*, 2007.

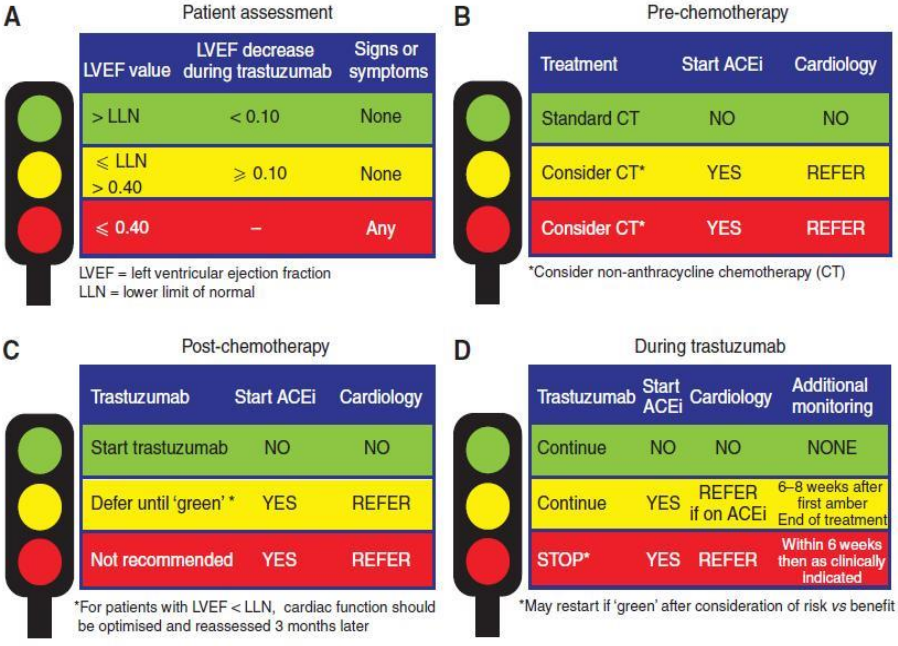

Figure 2 Traffic light system to prevent, monitor, and manage cardiac events in patients undergoing cytotoxic chemotherapy. (**A**) Patient assessment during trastuzumab therapy; (**B**–**D**) indications for ACEi therapy and referral to a cardiologist before (**B**) and after (**C**) chemotherapy, and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

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