Systemic Anti Cancer Treatment Protocol

EC – DH
Epirubicin, Cyclophosphamide followed by Docetaxel with Trastuzumab

PROTOCOL REF: MPHAECDHBR
(Version No: 1.1)

Approved for use in:

Adjuvant or Neo-adjuvant Breast: HER2 positive, fit and/or moderate/high risk patients.

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	100mg/m²	IV	Cycles 4 to 6 Day 1 only of a 21 day cycle
Trastuzumab	600mg	s/c	18 cycles in total, commencing at cycle 4 of chemotherapy Day 1 only of a 21 day cycle

<u>During COVID19 give consideration to 9 cycles of trastuzumab in patients with lower risk of recurrence and giving paclitaxel in preference to docetaxel to reduce risk of admission with neutropenic sepsis</u>

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 six

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

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

Docetaxel is exfoliant

Trastuzumab - None for the subcutaneous injection. Intravenous product considered to be neutral

Administration:

EC Cycles 1-3

Day	Drug	Dose	Route	Diluent and rate
1	**Ondansetron** 30mins before chemotherapy	**24mg**	**PO**	
	Dexamethasone 30mins before chemotherapy	**12mg**	**PO**	
	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 Cycles 4-6

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** 30mins before chemotherapy	**8mg**	**Oral**	
1	**Docetaxel**	**100mg/m^2**	**IV**	**250mL 0.9% sodium chloride over 60 minutes**

Repeat every 21 days for 3 cycles

The infusion volume for docetaxel may increase to 500mL depending on the dose to be administered

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 and then continued with the previously prescribed oral dexamethasone

Switch to paclitaxel

If severe toxicity from docetaxel, then consider switch to weekly paclitaxel with 3 weeks of weekly paclitaxel for each docetaxel dose.

Trastuzumab

To commence with cycle 4 (or weekly paclitaxel). Ensure ECHO measurement of LVEF has been undertaken.

For subcutaneous preparation:

Withdraw the contents of the vial into a 10mL syringe using 16g needle and then change the needle to a subcutaneous 24g needle prior to administering the dose

Day	Drug	Dose	Route	Diluent and rate
1	Trastuzumab	600mg	Subcutaneous injection	Over 2 to 5 minutes

Considerations:

The injection site should be alternated between the left and right thigh

New injections should be given at least 2.5cm from the old site and never into areas where the skin is red, bruised, tender or hard

Following administration of the first dose, monitor for 2 hours after for hypersensitivity reactions.

For intravenous preparation:

Day	Drug	Dose	Route	Diluent and rate
1	Trastuzumab	8mg/kg loading dose	IV	In 250mL sodium chloride 0.9% Over 90 minutes
From cycle 2 onwards:				
1	Trastuzumab	6mg/kg maintenance dose	IV	In 250mL sodium chloride 0.9% over 30 to 60 minutes as tolerated

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. Trastuzumab – cardiotoxic, requires monitoring, see separate section
Respiratory	Acute respiratory distress syndrome, pneumonitis

Dermatological	Alopecia, normally reversible, although can be permanent 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. 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	Cycle 6	Comments
Medical Assessment	X		X		X		X	Alternate cycles. Then for assessment every 3 months whilst on trastuzumab
Nursing Assessment	X	X	X	X	X	X	X	Every cycle
ECHO / ECG	X			X				Then every 4 months 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
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 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 febrile neutropenia: 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

Hepatic impairment:

	Epirubicin	Cyclophosphamide
Bilirubin µmol/L	**Dose**	**Dose**
24 to 50	50%	100%
51 to 85	25%	75%
>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 G2) 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

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.

Cardiac Toxicity

Cardiac toxicity should be managed used the NCRI recommendations reproduced below:

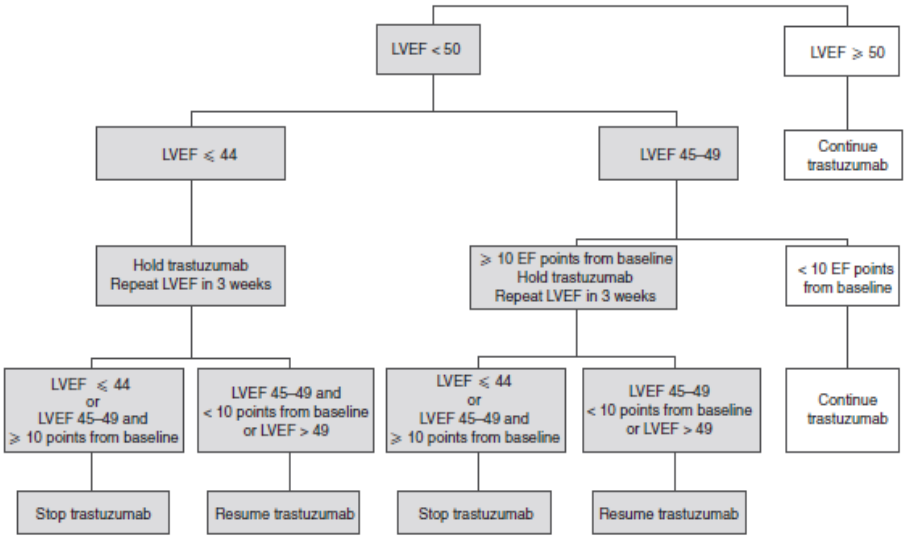

Figure 1 Current recommendations for cardiac monitoring in trastuzumab-treated patients (reproduced from Suter *et al*, 2007; online Appendix only). Reproduced with permission of the American Society of Clinical Oncology, from Suter *et al*, 2007.

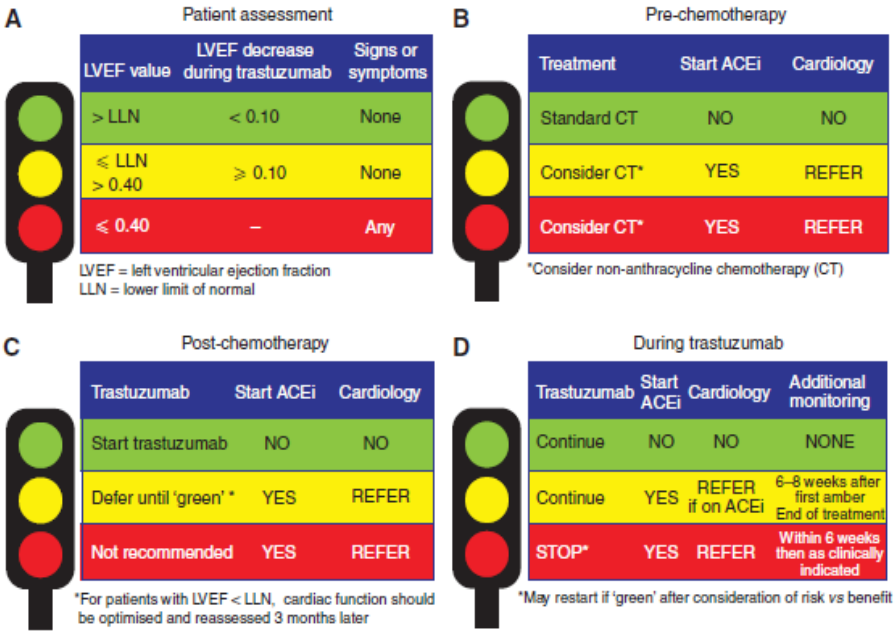

Figure 2 Traffic light system to prevent, monitor, and manage cardiac events in patients undergoing cytotoxic chemotherapy. (**A**) Patient assessment during trastuzumab therapy; (**B**–**D**) indications for ACEi therapy and referral to a cardiologist before (**B**) and after (**C**) chemotherapy, and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

References:

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