Systemic Anti Cancer Treatment Protocol

Paclitaxel and Trastuzumab Breast Cancer

PROTOCOL REF: MPHAPTRBR
(Version No: 1.2)

Approved for use in:

HER2 positive breast cancer. For adjuvant use in T1 or T2 (up to 3cm) N0/N1 and/or less fit patients.

Dosage:

Drug	Dosage	Route	Frequency
Paclitaxel	80mg	IV	Every 7 days
Trastuzumab	600mg	SC	Every 21 days

Adjuvant Treatment

Paclitaxel repeated weekly for 12 weeks. Trastuzumab repeated 3 weekly for 18 cycles.

During COVID-19 give consideration to 9 cycles of trastuzumab in patients with lower risk of recurrence.

There is also the option in COVID-19 contingency arrangements for trastuzumab single agent to be administered as adjuvant treatment if clinically appropriate.

Supportive treatments

Domperidone tablets, 10mg three times a day when required

Extravasation risk:

Paclitaxel - vesicant.

Trastuzumab s/c – no risk of extravasation.

Interactions

The metabolism of paclitaxel is catalysed, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Use with caution when administering paclitaxel concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

Administration:

Paclitaxel

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone	8mg	IV	30 minutes before chemotherapy Reduce to 4mg from week 2
	Famotidine	20mg	Oral	At least 60 minutes before chemotherapy (can be discontinued after three cycles for those patients who do not experience a drug hypersensitivity reaction).
	Chlorphenamine	10mg	IV	30 minutes before chemotherapy
	Paclitaxel	**80mg/m^2**	**IV**	**250 to 500mL sodium chloride 0.9% over 60 minutes** using a non-PVC giving set with a 0.22 micron filter

Repeat every 7 days for 12 weeks.

Trastuzumab

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

Repeat every 21 days for 18 cycles

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.

Main Toxicities:

Haematological	Neutropenia, anaemia, thrombocytopenia
Gastrointestinal	Diarrhoea, vomiting, nausea, mucositis
Cardiotoxicity	Congestive heart failure is a common adverse effect associated with trastuzumab. See separate cardiac toxicity below for further details. Bradycardia, myocardial infarction, AV block and syncope, cardiomyopathy, asymptomatic ventricular tachycardia
Dermatological	Alopecia, normally reversible Paclitaxel: Brittle, chipped and ridged nails
Ocular	Watery eyes, gritty and irritated

Hypersensitivity reactions	Reactions may occur within a few minutes following the initiation of treatment with paclitaxel, 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 paclitaxel and appropriate treatment. Patients who have developed severe hypersensitivity reactions should not be re-challenged with paclitaxel. 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	Paclitaxel: peripheral neuropathy is very common
Musculoskeletal	Arthralgia, myalgia common with paclitaxel
Infertility	Amenorrhea, risk of premature menopause However ensure appropriate contraceptive advice is given

Investigations and Treatment Plan:

	Pre	Wk1	Wk2	Wk3	Ongoing
Medical Assessment	X				Every 6 weeks during paclitaxel,and every 3 months whilst on trastuzumab.
Nursing Assessment		X	X	X	Every cycle
FBC	X	X	X	X	Every week during paclitaxel
U&E & LFTs	X	X	X	X	Every week during paclitaxel
ECHO	X				Every 4 months whilst on trastuzumab.
CT scan	X				As clinically indicated
Informed Consent	X				
Blood pressure measurement	X	X	X	X	As clinically indicated
PS recorded	X	X	X	X	
Toxicities documented	X	X	X	X	
Weight recorded	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

For patients with grade 2 toxicity refer to consultant for review and consideration of dose reduction

Haematological Toxicity during paclitaxel:

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: 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:

Bilirubin less than 1.25 times ULN and AST < 10 x ULN	Give 100% dose paclitaxel
Bilirubin greater than 1.25 times ULN	Consider dose reduction of paclitaxel
Alk Phos more than 3 times ULN	Consider dose reduction of paclitaxel

Renal impairment:

No dose adjustments required for moderate renal impairment.

Peripheral Neuropathy

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

If NCI-CTC grade 3 (or persistent G2) peripheral neuropathy occurs, discontinue

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.

FBC is not required prior to treatment

- 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- Trastuzumab:

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

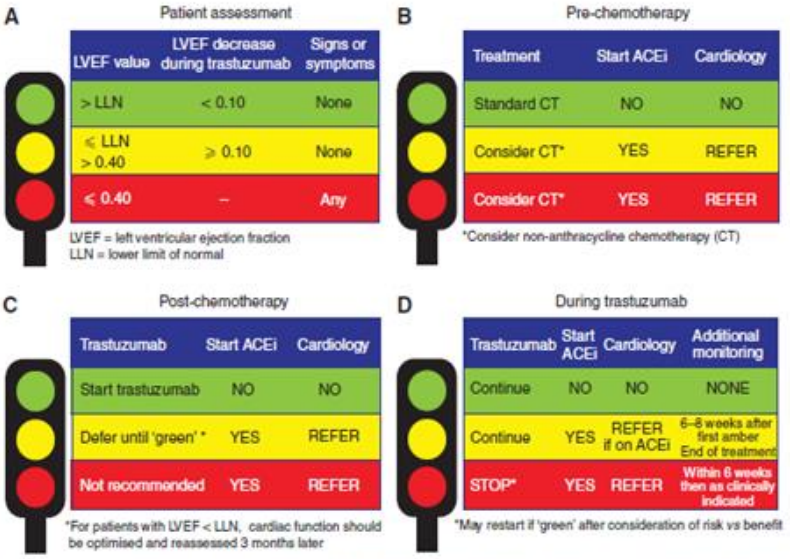

Figure 2 Traffic light system to prevent, monitor, and manage cardiac events in patients undergoing cytotoxic chemotherapy. (**A**) Patient assessment during trastuzumab therapy; (**B**–**D**) indications for ACEi therapy and referral to a cardiologist before (**B**) and after (**C**) chemotherapy, and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

References

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