PROTOCOL

Systemic Anti-Cancer Therapy Protocol

Paclitaxel and Trastuzumab Compassionate Use HER 2 positive salivary gland carcinoma

PROTOCOL REF: MPHAPTSGC
(Version No. 1.0)

Approved for use in:

- Compassionate use for a single patient
- HER 2 positive salivary gland carcinoma

Dosage:

Drug	Dose	Route	Frequency	
Paclitaxel	**80 mg/m^2**	IV infusion	Day 1, 8, 15 of a 21 day cycle	
Trastuzumab	**8 mg/kg**	IV infusion	Day 1 Cycle 1 only	Loading dose
Trastuzumab	**6mg/kg**	IV infusion	Day 1 of 21 day cycle, cycle 2 onwards	

Treatment to progression, review after 4 cycles. Single agent trastuzumab can continue if paclitaxel stopped and vice versa.

Administration:

- Paclitaxel must be administered using a non-PVC giving set with a 0.22 micron filter.
- Paclitaxel in solution may show haziness which is attributed to the formulation of paclitaxel.

- Excessive shaking, agitation, or vibration of paclitaxel may induce precipitation and should be avoided
- Consider IV access and referral for PICC insertion

Emetogenic risk:

Mildly emetogenic

Supportive treatments:

Metoclopramide 10mg THREE times a day when required

Ondansetron 8mg orally pretreatment can be added in patients with nausea

Loperamide 4mg stat and then 2mg after each loose stool if diarrhea is a side effect

Extravasation risk:

Paclitaxel - vesicant.

Trastuzumab – non vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal	Paclitaxel Trastuzumab	No dose adjustment required

Hepatic	Paclitaxel	**Bilirubin and Transaminases**	**Percentage dose**
		Transaminases <10 x ULN and bilirubin ≤1.25 x ULN	Dose at 100%
		Transaminases <10 x ULN and bilirubin >1.25 – 2 x ULN	80%
		Transaminases <10 x ULN and bilirubin 2-5 x ULN	50%
		Transaminase ≥10 x ULN or bilirubin >5 x ULN	Contraindicated
	Trastuzumab	No dose adjustments required	

Patients with severe hepatic impairment must not be treated with paclitaxel.

Patients with hepatic impairment may be at increased risk of paclitaxel toxicity, particularly grade III-IV myelosuppression. There is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. No data are available for patients with severe baseline cholestasis.
Patients should be monitored closely for the development of profound myelosuppression.

Interactions:

Paclitaxel:-

Antiepileptics (CYP 3A4 inducers)

Phenytoin, carbamazepine and phenobarbital increase the clearance of paclitaxel and increase its maximum tolerated dose.

Ciclosporin

Levels of paclitaxel increased after oral administration of ciclosporin.

Fluconazole/Ketoconazole (CYP3A4 inhibitors)
Paclitaxel levels may be increased

Quinine and Verapamil
Paclitaxel levels possibly increased.

For more detailed interactions please refer to the SPC

https://www.medicines.org.uk/emc/product/3891/smpc#gref

Trastuzumab –

None observed

Treatment schedule:

Cycle 1

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone	6.6mg	IV	30 minutes before treatment
	Chlorphenamine	10mg	IV	30 minutes before treatment
	Paracetamol	1000mg	PO	30 minutes before treatment
	Trastuzumab	**8mg/kg**	**IV**	**250mL sodium chloride over 90 minutes**
	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
8, 15	Dexamethasone	3.3mg	IV	30 minutes before chemotherapy
	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

Cycle 2 onwards

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone	3.3mg	IV	30 minutes before treatment
	Chlorphenamine	10mg	IV	30 minutes before treatment
	Paracetamol	1000mg	PO	30 minutes before treatment

	Trastuzumab	**6mg/kg**	**IV**	250mL sodium chloride over 60 minutes at cycle 2, and then 30 minutes thereafter if well tolerated
	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
8, 15	Dexamethasone	6.6mg	IV	30 minutes before treatment
	Chlorphenamine	10mg	IV	30 minutes before treatment
	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

- Premedication treatment of chlorphenamine and dexamethasone is given prior to paclitaxel to reduce the risk of hypersensitivity. Paclitaxel reactions commonly occur within the first few minutes of starting the infusion most likely with the first two cycles. See hypersensitivity policy for more information
- Paracetamol can be discontinued if trastuzumab is well tolerated

Main toxicities:

Paclitaxel	
Haematological	Neutropenia, anaemia, thrombocytopenia,
Cardiac and Vascular disorders	Risk of bradycardia and hypotension is common
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, mucositis
Musculoskeletal	Arthralgia, myalgia
Nervous system	Paclitaxel: peripheral neuropathy is very common
Hepatobiliary	Elevation of liver transaminases, alkaline phosphatase and bilirubin.

Skin and subcutaneous tissue disorders	Alopecia Allergic skin rash frequently associated with pruritus
General disorders and administration site conditions	Malaise, fever, chills, urticaria, flu-like syndrome, rash, pruritus. Injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis)
Trastuzumab	
Cardiotoxicity	Congestive heart failure is a common adverse effect associated with trastuzumab. See separate cardiac toxicity below for further details.
Hypersensitivity reactions	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.
Other	Fatigue Pulmonary events – pneumonitis, occasionally fatal

Cardiotoxicity

- Sharp falls in LVEF (10 points or to <50%) during cytotoxic chemotherapy may indicate increased susceptibility to cardiac dysfunction on trastuzumab
- 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 should be managed used the NCRI recommendations reproduced below:**
    - **NCRI recommendations for cardiac monitoring**
    - **Ref: British Journal of Cancer 2009 100:684-692**

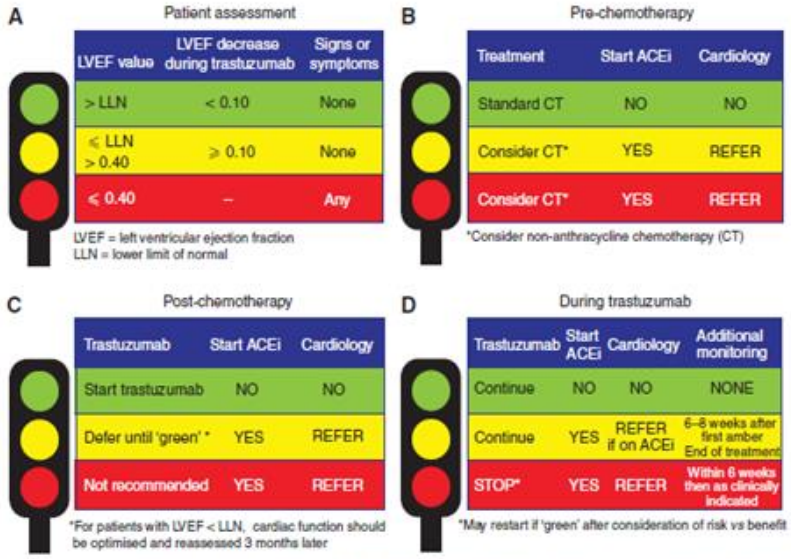

Figure 2 Traffic light system to prevent, monitor, and manage cardiac events in patients undergoing cytotoxic chemotherapy. (**A**) Patient assessment during trastuzumab therapy; (**B**–**D**) indications for ACEi therapy and referral to a cardiologist before (**B**) and after (**C**) chemotherapy, and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

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	X				
Clinical Assessment	X			X	At week 12 or earlier if clinically indicated
SACT Assessment (to include PS and toxicities)	X	X	X	X	Every cycle
FBC	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	Every Cycle
CT scan	X				At week 12 and if clinically indicated
ECG	X				Baseline

ECHO	X				Repeated every 3-4 months
Respiratory Rate					If clinically indicated
Weight recorded	X	X	X	X	Every cycle
Height recorded	X				

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if:

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Peripheral Neuropathy

Paclitaxel
CTCAE grade 2 peripheral neuropathy: withhold paclitaxel until the neuropathy recovers to grade 1 then dose reduce to 75% of the original dose. Further dose reduction to 60% if neuropathy returns. Where the peripheral neuropathy is ≥grade 3 omit further paclitaxel.

Grading and Management of Toxicity

Toxicities should be graded according to the CTCAE v4.0 criteria. Following assessment treatment should be withheld for any toxicity until resolved to grade 0/1. For dose modification, follow the general guidance below and discuss with treating clinician.

	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to ≤ grade 1, then continue at 100% of original dose with prophylaxis where possible	Interrupt treatment until resolved to grade ≤ 1, then continue at 80% of original dose	Discontinue treatment

2nd appearance	Interrupt treatment until resolved to grade ≤ 1, then continue at 80% of original dose	Interrupt treatment until resolved to grade ≤ 1, then continue at 50% of original dose	
3rd appearance	Interrupt treatment until resolved to grade ≤ 1, then continue at 50% of original dose	Discontinue treatment	
4th appearance	Discontinue treatment		

References:

1. https://www.medicines.org.uk/emc
2. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
3. BNF available via: https://bnf.nice.org.uk/

Circulation/Dissemination

Date added into Q-Pulse	9th November 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
August 2023	1.0	**Lisa Dobson** **Lung SRG Pharmacist**	New Regimen Protocol