Systemic Anti Cancer Treatment Protocol

Trastuzumab, Cisplatin & Capecitabine (HCX or HCarboX) Gastric

PROTOCOL REF: MPHAUGIHCX
(Version No: 1.2)

Approved for use in:

First line treatment of HER2 positive (IHC3+ or FISH positive) metastatic adenocarcinoma of the stomach or gastro-oesophageal (GoJ) junction.
PS 0-1

Dosage:

Cycles 1 to 6

Drug	Dosage	Route	Frequency
Trastuzumab	8mg/kg	IV infusion	Day 1 cycle 1 only
Trastuzumab	6mg/kg	IV infusion	Cycle 2 onwards* Every 21 days
Cisplatin	80mg/m^2	IV infusion	Every 21 days
Capecitabine	1000mg/m^2 BD for 14 days	PO	Every 21 days

***** If ≥ 6 weeks from last dose due to treatment delay then will required 8mg/kg loading dose

Carboplatin should be used as an alternative to Cisplatin in patients with a Creatinine Clearance (CrCl) calculated using Cockroft and Gault (C&G) formula < 60ml/min or in case of deafness.

Drug	Dosage	Route	Frequency
Carboplatin	AUC5	IV infusion	Every 21 days

5FU pump can used as an alternative in patients unable to tolerate capecitabine.

Drug	Dosage	Route	Frequency
Fluorouracil (1000mg/m^2/day for 4 days)	**4000mg/m^2**	IV	Continuous infusion over 96 hours in LV2 pump with sodium chloride 0.9% to 195mL

Cycle 7 onwards

Drug	Dosage	Route	Frequency
Trastuzumab	6mg/kg If ≥ 6 weeks from last dose due to treatment delay then 8mg/kg loading dose will be required	IV infusion	Every 21 days

Repeat every 21 days until disease progression or unacceptable toxicity

Supportive treatments:

Aprepitant 80mg orally once a day on days 2 and 3

Dexamethasone 4mg orally twice a day for 3 days

Metoclopramide 10mg oral tablets, up to 3 times a day or as required

Loperamide 2mg when required after each loose stool

Counselling Points:

Capecitabine

- Tablets should be taken 12 hours apart, swallowed whole with plenty of water within 30 minutes of a meal.
- Do not add doses missed due to toxicity onto the end of the cycle. Continue according to the treatment plan and stop taking on the originally scheduled day.
- Take missed doses if remembered within 2 hours of the normal scheduled time. Otherwise continue with the next scheduled dose. Do not double up missed doses
- **In case of swallowing difficulties** the tablets may be dissolved in 200ml warm water. Once dissolved stir the contents with a spoon and drink immediately. Wash well and reserve the glass and spoon for chemotherapy administration only.

Trastuzumab

- Beware infusion related reactions and observe patients for at least 2 hours after the start of the first trastuzumab loading dose.
- Occasionally delayed reactions including pulmonary symptoms will occur more than 6 hours after the infusion and patients should be made aware of this and advised to contact the help line if symptoms occur.

Extravasation risk:

Trastuzumab – neutral

Cisplatin – irritant

Carboplatin- irritant

Fluorouracil- irritant

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

Drug Interactions

Capecitabine

Phenytoin – potentially toxic levels of phenytoin have been reported- monitor carefully

Warfarin and other coumarin anticoagulants – increased bleeding risk, monitor INR carefully, consider switch to LMWH

Sorivudine and analogues – Potentially fatal interaction – avoid completely

Allopurinol – reduced efficacy of capecitabine – avoid

Main Toxicities:

General regimen associated toxicities	Myelosuppression, alopecia, renal impairment, nausea and vomiting, stomatitis, ovarian failure/infertility, cardiotoxicity
Cisplatin	Neuropathy, ototoxicity, nephrotoxicity

Capecitabine / Fluorouracil:	DPD deficiency – leads to severe early fluorouracil/capecitabine toxicity, affects approximately 3% of population, may be life threatening. Diarrhoea, PPE **Caution** in patients with pre-existing heart disease, angina pectoris, arrhythmias or taking high dose aspirin or coumarin anticoagulants
Trastuzumab	Infusion related symptoms (mild to moderate): fever, chills, headache, nausea, rash, arthralgia, myalgia (usually occur with 1st dose)

Administration:

Cisplatin regimen cycles 1 to 6

Day	Drug	Dosage	Route	Diluent and Rate
1	**Aprepitant** 30 minutes prior to chemotherapy	125mg	PO	With 80mg on days 2 and 3
1	**Dexamethasone** 30 minutes prior to chemotherapy	12mg	PO	
1	**Ondansetron** 30 minutes prior to chemotherapy	24mg	PO	
1	**Paracetamol** 30 minutes prior to trastuzumab	1000mg	PO	
1	**Trastuzumab**	8mg/kg cycle 1 ONLY* 6mg/kg cycle 2 onwards	IV	In 250mL Sodium Chloride 0.9% Over 90 minutes for 1st dose, then 60 minutes for 2nd dose thereafter over 30 minutes if tolerated
1	Furosemide	20mg	PO	
1	Sodium Chloride 0.9% with 20mmol	1000mL	IV	Over 90 minutes

	potassium chloride			
1	Monitor urine output – see notes below			
1	**Cisplatin**	80mg/m^2	IV	In 1000mL Sodium Chloride 0.9% over 90 minutes
	Sodium Chloride 0.9% with 20mmol potassium chloride	1000mL	IV	Over 90 minutes
1 to 14	**Capecitabine**	1000mg/m^2 Twice Daily	PO	Morning and evening for 14 days with 7 days off

OR

Alternative carboplatin regimen C1 to 6

Day	Drug	Dosage	Route	Diluent and Rate
1	**Dexamethasone** 30 minutes prior to chemotherapy	8mg	PO	
1	**Ondansetron** 30 minutes prior to chemotherapy	16mg	PO	
1	**Paracetamol** 30 minutes prior to trastuzumab	1000mg	PO	
1	**Trastuzumab**	8mg/kg cycle 1 ONLY* 6mg/kg cycle 2 onwards	IV	In 250mL Sodium Chloride 0.9% Over 90 minutes for 1st dose, then 60 minutes for 2nd dose thereafter over 30 minutes if tolerated
1	Sodium Chloride 0.9% flush	50ml	IV	Flush
1	**Carboplatin**	AUC5	IV	In 500mL Glucose 5% over 60 minutes
1	Sodium Chloride 0.9% flush	100ml	IV	Flush
1 to 14	**Capecitabine**	1000mg/m^2 Twice Daily	PO	Morning and evening for 14 days with 7 days off

Repeat every 21 days

Administration Notes:

Trastuzumab

* If ≥ 6 weeks from last dose due to treatment delay then 8mg/kg loading dose will be required

Cisplatin

- Calculate creatinine clearance using Cockcroft and Gault (C&G) equation (application for calculating creatinine using C&G formula is available on the Remote Citrix Web Portal) ahead of each cycle of treatment:

  Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

  Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

- Pre-hydration fluids should be administered immediately before cisplatin infusion is started and post hydration fluids should be administered immediately after cisplatin infusion has finished – There should **NOT** be any gaps in treatment.
- **Do not start cisplatin infusion unless urine output is at least 100mL/hour estimated from the previous 3 hours**. If necessary, administer further 500mL 0.9% sodium chloride and furosemide 20mg orally.
- The patient should be asked to drink 2 litres of fluid over 24 hours after the infusion and should contact the unit immediately if unable to do so for any reason.

Carboplatin

Meditech calculates creatinine clearance/GFR using the Wright formula (application for using Wright formula is available on the Remote Citrix Web Portal). Please refer to 'Carboplatin Dosing Calculator' SOP outlining process for checking carboplatin dose ahead of each cycle of treatment.

Calvert formula for Carboplatin dosage-:

Carboplatin dose in mg = AUC x (GFR or CrCl + 25)

As with all platinum based chemotherapy, patients may experience allergic reaction during administration. Please refer to the CCC Hypersensitivity; Management Prevention Policy.

For severe reactions, discuss with Consultant before continuing with treatment. It should be strongly noted that patients who have severe reactions should not be re-challenged.

Cycle 7 onwards

Day	Drug	Dosage	Route	Diluent and Rate
Day1	**Trastuzumab**	6mg/kg If ≥ 6 weeks from last dose due to treatment delay then 8mg/kg loading dose will be required	IV	In 250mL Sodium Chloride 0.9% over 30 minutes

Repeat every 21 days until disease progression or unacceptable toxicity

HCF regimen- alternative regimen with infusional fluorouracil if capecitabine cannot be administered.

Cisplatin regimen cycles 1 to 6

Day	Drug	Dosage	Route	Diluent and Rate
1	**Aprepitant** 30 minutes prior to chemotherapy	125mg	PO	With 80mg on days 2 and 3
1	**Dexamethasone** 30 minutes prior to chemotherapy	12mg	PO	
1	**Ondansetron** 30 minutes prior to chemotherapy	24mg	PO	

1	**Paracetamol** 30 minutes prior to trastuzumab	1000mg	PO	
1	**Trastuzumab**	**8mg/kg** cycle 1 **6mg/kg** cycle 2 onwards	IV	In 250mL Sodium Chloride 0.9% Over 90 minutes for 1st dose, then 60 minutes for 2nd dose and 30 minutes thereafter as tolerated
1	Furosemide	20mg	PO	
1	Sodium Chloride 0.9% with 20mmol potassium chloride	1000mL	IV	Over 90 minutes
1	Monitor urine output – see notes below			
1	**Cisplatin**	**80mg/m^2**	IV	In 1000mL Sodium Chloride 0.9% over 90 minutes
	Sodium Chloride 0.9% with 20mmol potassium chloride	1000mL	IV	Over 90 minutes
1 to 4	**Fluorouracil** (1000mg/m^2/day for 4 days)	**4000mg/m^2**	IV	Continuous infusion over 96 hours in LV2 pump with sodium chloride 0.9% to 195mL

Repeat every 21 days

OR

HCarboF - Alternative regimen with Carboplatin 5FU for Cycle 1 to Cycle 6

Day	Drug	Dosage	Route	Diluent and Rate
1	**Dexamethasone** 30 minutes prior to chemotherapy	8mg	PO	
1	**Ondansetron** 30 minutes prior to chemotherapy	16mg	PO	
1	**Paracetamol** 30 minutes prior to trastuzumab	1000mg	PO	
1	**Trastuzumab**	8mg/kg cycle 1 6mg/kg cycle 2 onwards	IV	In 250mL Sodium Chloride 0.9% Over 90 minutes for 1st dose, then 60 minutes for 2nd dose thereafter over 30 mins if tolerated
1	Sodium Chloride 0.9% flush	50ml	IV	Flush

1	**Carboplatin**	AUC5	IV	In 500mL Glucose 5% over 60 minutes
1	Sodium Chloride 0.9% flush	100ml	IV	Flush
1 to 4	**Fluorouracil** (1000mg/m^2/day for 4 days)	**4000mg/m^2**	IV	Continuous infusion over 96 hours in LV2 pump with sodium chloride 0.9% to 195mL

Repeated every 21 days

Cycle 7 onwards

Day	Drug	Dosage	Route	Diluent and Rate
Day1	**Trastuzumab**	6mg/kg	IV	In 250mL Sodium Chloride 0.9% over 30 minutes

Repeat every 21 days until disease progression or unacceptable toxicity

Investigations and treatment plan

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Medical Assessment	X		X		X	Alternate cycles
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	Every cycle
MUGA / ECHO	X				X	Every 3 to 4 months **Baseline LVEF ≥ 50% for trastuzumab to proceed**
FBC	X	X	X	X	X	Every cycle to cycle 6
U&E, LFT, Serum magnesium and calcium	X	X	X	X	X	Every cycle to cycle 6
CrCl Cisplatin- C&G formula Carboplatin- Wright formula	X	X	X	X	X	Every cycle to cycle 6 Refer to 'Administration' section for full details.
Dihydropyrimidine dehydrogenase (DPD) deficiency test	X					This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with **known complete DPD deficiency***.
CT scan	X				X	Every 12 weeks of as clinically indicated
Informed Consent	X					
ECG	X					As clinically indicated Capecitabine/ fluorouracil to be used with caution in patients with pre-existing heart disease, angina pectoris, arrhythmias or taking high dose aspirin or coumarin anticoagulants (refer to interactions section)
Full set of observations	X					Then as clinically indicated
Weight recorded	X	X	X	X	X	Every cycle

Height recorded	X					

For HCF regimen blood tests are not required on day 8 and day 15.

During treatment with Cisplatin and for a minimum of the following 6 months, appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes.

*DPD deficiency – leads to severe early fluorouracil toxicity, affects approximately 3% of population, may be life threatening

Dose Modifications and Toxicity Management:

Haematological toxicity

Cycles 1 to 6

Proceed on day 1 if:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Delay 1 week on day 1 and dose reduce cisplatin and capecitabine by 20% if:-

ANC ≤ 0.9 x 10^9/L	Platelets ≤ 99 x 10^9/L

Trastuzumab dose is not modified for toxicity instead treatment is omitted at the discretion of the clinical team.

If cisplatin specific toxicities then can be switched to carboplatin at the discretion of the clinical team.

Cycle 7 onwards

For ongoing single agent trastuzumab blood tests are not required

Haematological and Non-haematological Capecitabine dose adjustment

Haematological Toxicity / Grades	**Dose changes within a treatment cycle**	**Dose adjustment for next cycle/dose (% of starting dose)**
• *Grade 1*	Maintain dose level	Maintain dose level
• *Grade 2*		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance		75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	Not applicable
• *Grade 3*		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	Not applicable
• *Grade 4*		

-1st appearance	Discontinue permanently *Or* If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
-2nd appearance	Discontinue permanently	Not applicable

Non-haematological toxicity

Diarrhoea	Treat symptomatically with loperamide at standard doses, codeine may be added. If persistent or grade 3 or 4 stop capecitabine until resolved to grade 0 or 1. Restart as per CTC table above for dose reductions
Stomatitis	Regular mouthwashes (water, saline or non alcoholic proprietary brand), brush gently with a soft brush, adequate pain relief, nutritional support in severe cases – see above for dose reductions.
PPE	Manage as per trust policy, withhold treatment until resolved to grade 1, dose reductions as per CTC table above.
Conjunctivitis	Eye drops for symptomatic treatment
Chest Pain / coronary artery spasm	Stop capecitabine, standard angina investigations, refer to consultant, if symptoms persist stop capecitabine permanently

Renal

Both cisplatin and carboplatin are eliminated primarily in the urine and are themselves nephrotoxic. If there is any significant renal toxicity discuss with consultant before proceeding.
Ahead of each cycle of treatment calculate CrCl/GFR using (refer to 'Administration' Section:

- C&G formula prior to treatment with cisplatin.
- Wright formula prior to treatment with carboplatin.

GFR (mL/min)	Cisplatin dose	Carboplatin dose	Capecitabine dose
≥ 60	100%	100%	100% dose
50 to 59	75% OR Consider switching to carboplatin		100% dose
30 to 49	Switch to carboplatin	**If CrCl ≤ 20ml/min Discuss with clinical team prior to administration**	75% dose
< 30			Omit

Hepatic

Cisplatin
No modifications needed

Capecitabine
No dose adjustment required for hepatic impairment at baseline BUT if bilirubin increases to 3 times ULN or ALT/AST to 2.5 times ULN subsequent to treatment then omit capecitabine until liver function recovers

Fluorouracil
Mild (bilirubin >1.0-1.5 x ULN and any AST or bilirubin ≤ULN and AST >ULN) and moderate (bilirubin 1.5-3 x ULN, with normal or raised AST)- no dose adjustment
Severe (bilirubin >3.0-10 x ULN, with normal or raised AST)- not recommended

References:

NICE TA 208 Trastuzumab for the treatment of HER2-positive metastatic gastric cancer. Published: 24 November 2010.

TOGA trial Lancet 2010 376(9742): p687

The Lancet: Dose recommendations for anticancer drugs with renal or hepatic impairment 2019