NHS
North West Coast
Strategic Clinical Networks

Chemotherapy protocol

Drug regimen
HCX

Indications for use
Locally advanced or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction
Tumours must be Her2 positive either 3+ on IHC or 2+ on IHC and positive on FISH (or similar)

Regimen

Drug	Fluid	Time
Trastuzumab 8mg/kg cycle 1 only; 6mg/kg on subsequent cycles	250ml 0.9% sodium chloride	See below
	1 litre 0.9% sodium chloride + 20mmol potassium chloride + 10mmol magnesium sulphate	2 hours
Cisplatin 80mg/m^2	1 litre 0.9% sodium chloride	2 hours
	1 litre 0.9% sodium chloride + 20mmol potassium chloride + 10mmol magnesium sulphate	2 hours

Capecitabine 625mg/m^2 bd orally days 1-21

Regimen to be repeated 3 weekly for 6 cycles in locally advanced or metastatic disease
Trastuzumab to be continued until disease progression
Trastuzumab should be administered over 90 minutes in cycle 1 then over 30 minutes for subsequent cycles. Patients should be observed closely for infusion related side effects or anaphylaxis during cycle 1.

Investigation prior to initiating treatment
FBC
Biochemical profile
Calculated creatinine clearance (Cl_{Cr})
Assessment of LVEF within the normal range on ECHO or MUGA - measured at least 4 monthly

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle). Patients require DPD testing prior to administration. Dose adjustments should be made in accordance with local DPD policy.

Cautions
Caution if history of ischaemic heart disease
Raised bilirubin or AST

Contra-indication
Patients experiencing dyspnoea at rest due to either co-morbidities or complications of advanced malignant disease should *not* receive trastuzumab.

Investigations and consultations prior to each cycle
FBC, U&Es, creatinine clearance (calculated), LFTs
The liver function test may be retrospectively looked at (i.e. after the chemotherapy treatment) **unless** they are known to be abnormal then they need to be repeated the day before so that the results are available pre-chemotherapy

Acceptable limits for treatment to proceed (if outside these delay one week or contact consultant)
Neutrophils >1.0 and platelets >75
Creatinine Clearance >50ml/min
Bilirubin <1.5 x ULN, ALT, AST < 2.5 ULN, Alk Phos < 2.5 ULN

Side Effects

Infusion related:
Mild – Chills and rigor, tumour site pain, nausea and vomiting, asthenia, headache, cardiotoxicity.
Severe – Dyspnoea, hypotension, urticaria/angioedema, anaphylaxis
Alopecia, Nephrotoxicity, Tiredness, diarrhoea and abdominal pain, nausea and vomiting, sore mouth, poor appetite, myelosuppression and thrombocytopenia, hand foot syndrome, cardiotoxicity (including coronary artery spasm, angina and tachycardia), ocular toxicity (excessive lacrimation, visual change, photophobia), peripheral neuropathy, infusion reactions, pulmonary fibrosis, veno-occlusive disease, high tone and hearing loss, ovarian failure/infertility

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism- avoid use in patients with known DPD deficiency

Dose Modification Criteria

Haematological Toxicity

Neutrophils ($x10^9$/l)	**Platelets ($x10^9$/l)**	**Action**
>1.0	> 100	Full Dose
<1.0	<100	Delay until recovery Restart capecitabine and cisplatin at 75% dose
<0.5 and febrile requiring hospitalisation		Delay until recovery Restart capecitabine and cisplatin at 50% dose

Renal

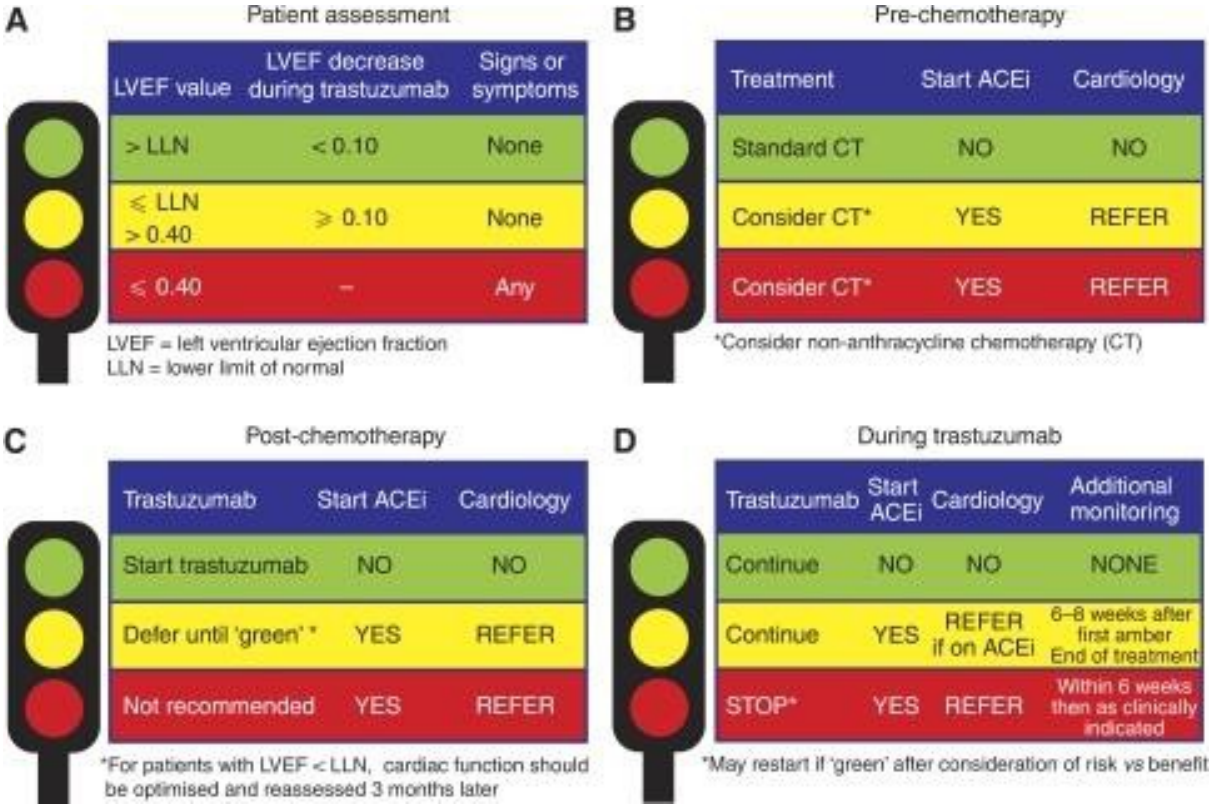
Result	**GFR (ml/min)**	**Action**
Trastuzumab		No dose reduction necessary
Cisplatin	<50	Defer and consider carboplatin AUC 5 if this remains low
Capecitabine	30-50	Dose reduce by 25%
	<30	Omit

Palmar-plantar erythema (PPE):

Palmar Plantar Erythrodysaesthesia	Grade	Action
	1	No dose reduction necessary
	2	Delay capecitabine until resolved to grade 0-1 then restart at 15% dose reduction
	3	Delay capecitabine until resolved to grade 0-1 then restart at 30% dose reduction

Cardiac Toxicity

Follow UK guidelines



Non-haematological toxicity: stomatitis, diarrhoea, nausea & vomiting

(See separate section for palmar-plantar syndrome)

For grade 2-3 toxicity, stop capecitabine and administer appropriate symptomatic management. If toxicity is adequately controlled with symptomatic measures alone within 2 days, then capecitabine may be restarted at 100% full dose. If toxicity persists, the following dose reductions should be made:

	Grade 2	**Grade 3**	**Grade 4**
1st appearance	Interrupt treatment until resolved to grade 0-1 then continue at same dose. .	Interrupt treatment until resolved to grade 0-1 then continue at 75% of original dose with prophylaxis where possible	Discontinue treatment unless consultant considers it to be in the best interest of the patient to continue at 50% of original dose once toxicity has resolved to grade 0-1.
2nd appearance of same toxicity	Interrupt treatment until resolved to grade 0-1 then continue at 75% of original dose	Interrupt treatment until resolved to grade 0-1 then continue at 50% of original dose	
3rd appearance of same toxicity	Interrupt treatment until resolved to grade 0-1 then continue at 50% of original dose	Discontinue treatment	
4th appearance of same toxicity	Discontinue treatment		

Consider HCF treatment (i.e. substituting 5FU for capecitabine) in patients with severe diarrhoea

<u>Specific Information on Administration</u>

Capecitabine tablets must be taken twice daily with food. Patients should be advised not to “double up” on missed doses and not to readminister any dose after vomiting
If the patient has difficulty swallowing, the capecitabine may be dispersed in water. Do not crush the tablets
Patients should be informed of the need to interrupt treatment immediately if they develop moderate or severe side effects particularly diarrhoea (not controlled by loperamide), palmar plantar erythrodyaesthesia, chest pain or infection.
Any unused tablets to be returned at the next appointment

References

Bang, Yung-Jue et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial The Lancet , Volume 376 , Issue 9742 , 687 - 697

Jones AL, et al -Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. Br. J. Cancer (2009)

THIS PROTOCOL HAS BEEN DIRECTED BY DR Mitchell DESIGNATED LEAD CLINICIAN FOR UPPER GI CANCER.

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

DATE **June 2017**

REVIEW **June 2019**

VERSION **7**