Chemotherapy Protocol

GASTROINTESTINAL (UPPER) CANCER

CISPLATIN-FLUOROURACIL-TRASTUZUMAB

Regimen

- Gastrointestinal (Upper) Cancer – Cisplatin-Fluorouracil-Trastuzumab

Indication

- Trastuzumab, in combination with cisplatin and fluorouracil is recommended as an option for the treatment of people with human epidermal growth factor receptor 2 (HER2) positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior treatment for their metastatic disease and who have tumours expressing high levels of HER2

- WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Cisplatin	Neuropathy, nephrotoxicity, ototoxicity
Fluorouracil	Palmar-plantar erythrodysesthesia, diarrhoea, chest pain
Trastuzumab	Cardio toxicity, acute respiratory distress syndrome, infusion related effects

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Regimen

- Prior to starting therapy confirm a positive HER2 status

- FBC, LFT's and U&E's prior to day one of treatment

- Cardiac function must be assessed prior to starting trastuzumab and twelve weekly thereafter unless there are signs of cardiac impairment where four to eight weekly may be more appropriate. If LVEF drops 10 ejection points from baseline and to below 50%, trastuzumab should be suspended and a repeat LVEF assessment performed within 21 days

- Patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with fluorouracil. All patients should be tested for DPD deficiency before initiation (cycle 1) to minimise the risk of these reactions

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Prior to prescribing the following criteria must be met.

Criteria	Eligible Level
Neutrophil	equal to or more than $1.5x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL

If the neutrophils are less than $1.5x10^9$/L and/or the platelets are less than $100x10^9$/L then delay treatment for 7 days and re-start treatment at the original dose. If a 14 day delay is required to allow counts to recover or there are two separate delays of 7 days during treatment the dose of the cisplatin should be reduced to 80% of the original dose.

There is little need to adjust the dose of trastuzumab for haematological toxicity.

Hepatic / Renal Impairment

Deteriorating liver or kidney function may be a sign of disease progression or drug toxicity.

Hepatic Impairment

Drug	Dose (% of original dose)
Cisplatin	No dose reduction necessary
Fluorouracil	If the bilirubin is more than 85umol/L and / or the AST more than 180umol/L fluorouracil is contra-indicated. In moderate hepatic impairment consider reducing the dose by 30% and for severe impairment by 50%
Trastuzumab	No dose reduction necessary

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cisplatin	more than 60	100
	45-59	75
	less than 45	Consider carboplatin
Fluorouracil	Consider dose reduction in severe renal impairment only	
Trastuzumab	No dose adjustment necessary	

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes. Dose limiting toxicities include diarrhoea, abdominal pain, emesis, stomatitis, palmar-plantar erythrodysesthesia and neurosensory toxicities among others.

In general if any NCI-CTC grade 1 toxicity occurs treatment should be continued, without interruption, at the full dose. For toxicities NCI-CTC grade 3 or above, in general, treatment should be withheld until recovery to at least NCI-CTC grade 1 then re-started if medically appropriate. If recovery takes twenty-one days or longer then stop treatment.

Cisplatin

Neurotoxicity occurring at a NCI-CTC grade 2 or above or a new functional deterioration in hearing and / or tinnitus that does not resolve between cycles should be approached by substituting the cisplatin for carboplatin.

Fluorouracil

Diarrhoea occurring for the first time at NCI-CTC grade 2 should be approached by withholding the fluorouracil until it has resolved to NCI-CTC grade 1 or below. Treatment can then be re-started at full dose. Treatment should again be delayed on development of a second NCI-CTC grade 2 or above diarrhoea and the fluorouracil re-started at 75% of the original dose when it has resolved to NCI-CTC grade 1 or below. After resolution of a third episode of NCI-CTC grade 2 diarrhoea to NCI-CTC grade 1 or below, the fluorouracil should be re-started using 50% of the original dose.

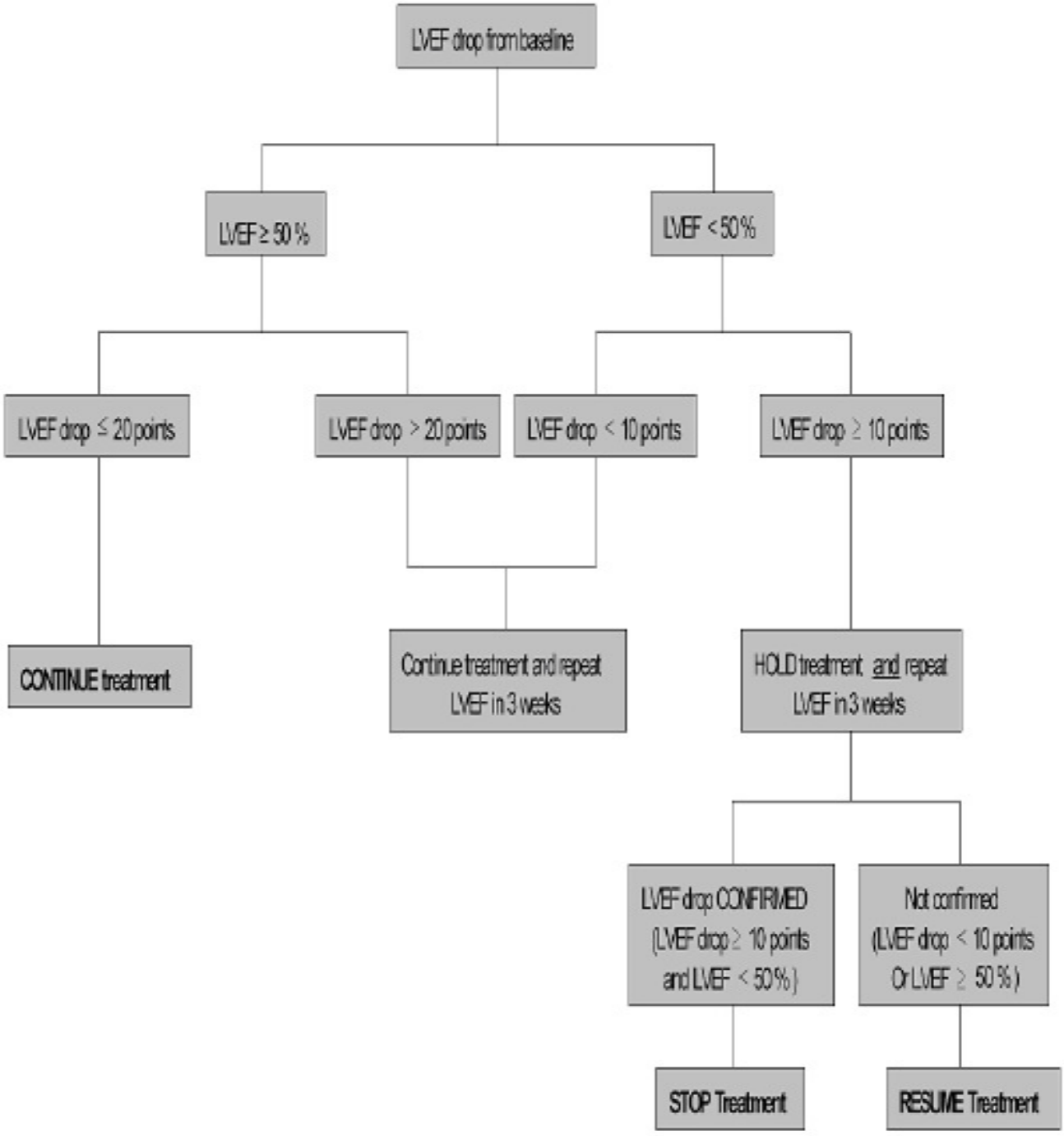
On appearance of a NCI-CTC grade 3 diarrhoea withhold fluorouracil until it has resolved to NCI-CTC grade 1 or below and re-start treatment using 75% of the original dose. After a second episode at NCI-CTC grade 3 wait until the diarrhoea has resolved to NCI-CTC grade 1 or below and resume the fluorouracil using 50% of the original dose. For a third appearance of NCI-CTC grade 3 diarrhoea or the development of NCI-CTC grade 4 toxicity at any time stop fluorouracil therapy.

Trastuzumab

The LVEF should be fifty or above before starting cycle one of trastuzumab.

Subsequent Echocardiograms

The flow chart below describes the process to be followed if there is an **asymptomatic** decline in LVEF during trastuzumab treatment.



Patients who develop **symptomatic** cardiac dysfunction should have trastuzumab discontinued, be commenced on ACE inhibitor therapy and be referred to a cardiologist. Further treatment should be discussed with the relevant consultant.

Regimen

21 day cycle for 6 cycles

The fluorouracil and cisplatin are given every 21 days for a maximum of 6 cycles. The trastuzumab is given until disease progression. Six cycles will be set in Aria after which the single agent trastuzumab regimen should be used.

Cycle One

Drug	Dose	Days	Route
Cisplatin	80mg/m^2	1	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin per minute (minimum 120 minutes)
Fluorouracil	1000mg/m^2/day (total dose 4000mg/m^2)	1, 2, 3, 4	Continuous intravenous infusion over 96 hours using an infusor device in sodium chloride 0.9%
Trastuzumab	8mg/kg	1	Intravenous Infusion in 250ml sodium chloride 0.9% over 90 minutes

Cycle Two Onwards

Drug	Dose	Days	Route
Cisplatin	80mg/m^2	1	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin per minute (minimum 120minutes)
Fluorouracil	1000mg/m^2/day (total dose 4000mg/m^2)	1, 2, 3, 4	Continuous intravenous infusion over 96 hours using an infusor device in sodium chloride 0.9%
Trastuzumab	6mg/kg	1	Intravenous Infusion in 250ml sodium chloride 0.9% over 30 minutes (if well tolerated at 90 minutes)

Dose Information

- Cisplatin will be dose banded in accordance with the national dose bands (1mg/ml)

- Fluorouracil will be dose banded in accordance with the national dose bands (50mg/ml)

- Trastuzumab will be dose rounded to the nearest 50mg (up if halfway)

- If the patient misses a dose of trastuzumab by fourteen days or less, then the usual maintenance dose of 6mg/kg should be given as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should be given according to the previous schedule

- If the patient misses a dose of trastuzumab by more than fourteen days, a re-loading dose of 8mg/kg should be given over 90 minutes. Subsequent maintenance doses should then be given every 21 days from that point

Administration Information

Extravasation

- Cisplatin – exfoliant

- Fluorouracil - inflamitant

- Trastuzumab – neutral

Other

- Central venous access and use of an ambulatory infusion pump is required

- Trastuzumab is associated with hypersensitivity reactions. Patients should be observed for six hours following the start of the first infusion of trastuzumab and for two hours following the start of subsequent infusions. If the patient has tolerated the first two infusions with no infusion related effects consideration can be given to reducing this observation period further

Additional Therapy

- Antiemetics prior to day **one** only

  15-30 minutes prior to chemotherapy

  - aprepitant 125mg oral
  - dexamethasone 4mg oral or intravenous
  - ondansetron 8mg oral or intravenous

  As take home medication;

  - aprepitant 80mg once a day oral for 2 days
  - dexamethasone 4mg once a day oral for 3 days
  - metoclopramide 10mg three times a day when required oral
  - ondansetron 8mg twice a day for 3 days oral

- Cisplatin pre and post hydration as follows;

Pre

Furosemide 40mg oral or intravenous

1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

Post

1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

Patients should be advised to drink at least 3 litres of fluid in the 24 hours after administration of cisplatin.

- For treatment of trastuzumab infusion reactions 'once only when required' doses of the following should be prescribed;

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous
  - paracetamol 1000mg oral

- Oral loperamide 4mg after the first loose stool then 2-4mg four times a day when required for the relief of diarrhoea (maximum 16mg/24 hours).

- Mouthwashes as per national or local guidelines for the treatment of mucositis

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

References

1. Bang YJ, Van Custem E, Fevereislova A et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for the treatment of HER2 positive advanced gastric or gastro-oesophageal junction cancer (TOGA): a phase 3, open label, randomised, controlled clinical trial. Lancet 2010; 376 (9742): 687-697.
2. National Institute for Health and Clinical Excellence (2010). NICE Technology Appraisal Guidance 208. Trastuzumab for the treatment of HER2-positive metastatic gastric cancer. DOH: London.

REGIMEN SUMMARY

Cisplatin-Fluorouracil-Trastuzumab

Day One Cycle One

1. Trastuzumab 8mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes.

2. Aprepitant 125mg oral

3. Dexamethasone 4mg oral or intravenous

4. Ondansetron 8mg oral or intravenous

5. Furosemide 40mg oral or intravenous

6. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

7. Cisplatin 80mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin/minute (minimum time 120 minutes)

8. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

9. Fluorouracil 4000mg/m^2 continuous intravenous infusion over 96 hours in sodium chloride 0.9%

10. Chlorphenamine 10mg intravenous when required for infusion related reactions

11. Hydrocortisone 100mg intravenous when required for infusion related reactions

12. Paracetamol 1000mg oral when required for infusion related reactions

Take Home Medicines

13. Aprepitant 80mg once a day for two days oral starting on day 2 of the cycle

14. Dexamethasone 4mg once a day for 3 days oral starting on day 2 of the cycle

15. Metoclopramide 10mg three times a day when required oral

16. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day 1 of the cycle

Day One Cycle Two Onwards

1. Trastuzumab 6mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes (if well tolerated at 90 minutes)

2. Aprepitant 125mg oral

3. Dexamethasone 4mg oral or intravenous

4. Ondansetron 8mg oral or intravenous

5. Furosemide 40mg oral or intravenous

6. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

7. Cisplatin 80mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin/minute (minimum time 120 minutes)

8. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

9. Fluorouracil 4000mg/m^2 continuous intravenous infusion over 96 hours in sodium chloride 0.9%

10. Chlorphenamine 10mg intravenous when required for infusion related reactions

11. Hydrocortisone 100mg intravenous when required for infusion related reactions

12. Paracetamol 1000mg oral when required for infusion related reactions

Take Home Medicines

13. Aprepitant 80mg once a day for two days oral starting on day 2 of the cycle

14. Dexamethasone 4mg once a day for 3 days oral starting on day 2 of the cycle

14. Metoclopramide 10mg three times a day when required oral

15. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day 1 of the cycle

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Nov 2020	Updated monitoring with DPD testing Dose banding updated Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.1	July 2014	Header changed Toxicities removed Pyridoxine removed from supportive therapies Mouthwashes updated Bolus removed throughout text Metoclopramide dose changed to 10mg Disclaimer added	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1	Feb 2012	None	Dr Deborah Wright Pharmacist	Dr Tim Iveson Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.