Chemotherapy Protocol

GASTROINTESTINAL (UPPER) CANCER

CAPECITABINE, CISPLATIN and EPIRUBICIN

(ECX)

Regimen

- Gastrointestinal Cancer (upper) – Capecitabine-Cisplatin-Epirubicin (ECX)

Indication

- First line therapy of advanced / metastatic eosophagogastric cancer
- Neoadjuvant therapy of potentially operable eosophagogastric cancer
- WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Capecitabine	Palmar-plantar erythrodysesthesia, diarrhoea, mucositis, chest pain
Cisplatin	Neuropathy, nephrotoxicity, ototoxicity
Epirubicin	Cardiac failure, urinary discolouration

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

Monitoring

Regimen

- Ensure adequate cardiac function before starting therapy. Baseline LVEF should be measured, particularly in patients with a history of cardiac problems or in the elderly.
- FBC, LFT's and U&E's prior to each cycle
- Patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with capecitabine. 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

For haematological toxicity without fever or infection, if the neutrophil count is less than 1×10^9/L or the platelet count less than 75×10^9/L, delay treatment until these levels are achieved. Treatment can be resumed using full doses provided the neutropenia was less than or equal to NCI-CTC grade 2 and the thrombocytopenia is less than or equal to NCI-CTC grade 1. For a NCI-CTC grade 3 neutropenia and / or a NCI-CTC grade 2 thrombocytopenia stop all treatment until recovery of counts. Then re-start the capecitabine and cisplatin at the last dose. The epirubicin should be reduced by 25%. For a NCI-CTC grade 4 neutropenia or NCI-CTC grade 3 thrombocytopenia again delay treament until counts have returned to acceptable levels. The capecitabine and cisplatin may be resumed at the last dose and the epirubicin reduced to 50%. If a NCI-CTC grade 4 thrombocytopenia occurs again delay treatment until full recovery occurs and then restart both the capecitabine and cisplatin at the last dose. Epirubicin should be stopped.

If at any time during a previous cycle an episode of neutropenic fever and / or sepsis has developed at NCI-CTC grade 3 then delay all chemotherapy until counts recover and re-start therapy using an epirubicin dose reduced by 25% of the previous cycles dose. This should be increased to 50% of the previous cycle's dose if the toxicity was NCI-CTC grade 4.

Dose reductions should apply to all future cycles.

Hepatic Impairment

Drug	Dose (% of original dose)
Capecitabine	There is little published information available. No dose reductions are necessary for those with mild to moderate hepatic dysfunction due to liver metastasis
Cisplatin	No dose reduction necessary
Epirubicin	If the bilirubin concentration is between 24-51umol/L reduce the dose by 50%. If the bilirubin concentration is more than 51 then administer 25% of the dose

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Capecitabine	More than 51	100
	30-50	75
	less than 30	Do not use
Cisplatin	more than 60	100
	45-59	75
	less than 45	Consider alternative
Epirubicin	Reduce doses in cases of severe impairment	

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 and palmar-plantar erythrodysesthesia among others.

Capecitabine

NCI-CTC Grade 2

Interrupt treatment until the toxicity resolves to NCI CTC grade 0-1 then continue at the same dose. If the toxicity recurs for a second time, again interrupt treatment until it resolves to NCI-CTC grade 0-1 then resume therapy using 75% of the original dose. If the same adverse effect develops on a third occasion once more interrupt treatment until it resolves to NCI-CTC grade 0-1 then continue at 50% of the original dose. Stop treatment if the toxicity re-appears on a fourth instance.

NCI-CTC Grade 3

Interrupt treatment until the toxicity resolves to NCI-CTC grade 0-1 then continue treatment using 75% of the original dose with prophylaxis if appropriate. If the toxicity recurs for a second time again interrupt treatment until it resolves to NCI-CTC grade 0-1 and then resume therapy at 50% of the original dose. If the same adverse effect develops on a third occasion discontinue capecitabine.

NCI-CTC Grade 4

Discontinue treatment unless the responsible consultant considers it to be in the best interest of the patient to continue at 50% of the original dose once the toxicity has resolved to NCI-CTC grade 0-1.

When capecitabine is stopped for toxicity the doses are omitted, not delayed.

Cisplatin

Neurotoxicity occurring at a NCI-CTC grade 2 or above or a new functional deterioration in hearing and / or tinnitus should be approached by substituting the cisplatin for carboplatin AUC5.

Regimen

21 day cycle for 8 cycles

Drug	Dose	Days	Route
Capecitabine	625mg/m^2 twice a day	1-21 incl	Oral
Cisplatin	60mg/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)
Epirubicin	50mg/m^2	1	Intravenous bolus over 10 minutes

Dose Information

- Capecitabine will be dose banded in accordance with the national dose bands
- Cisplatin will be dose banded in accordance with the national dose bands (1mg/ml)
- Epirubicin will be dose banded in accordance with the national dose bands (2mg/ml PM)

Administration Information

Extravasation

- Cisplatin - exfoliant
- Epirubicin - vesicant

Other

- Capecitabine should start on the evening of day 1.
- Capecitabine should be taken with or after food.

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy

  - dexamethasone 8mg oral or intravenous

- ondansetron 8mg oral or intravenous

As take home medication;

- dexamethasone 4mg twice a day for 3 days oral
- metoclopramide 10mg three times a day when required
- 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.

- 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

Additional Information

- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.

- Ensure the total daily dose of capecitabine is divided into two doses given twelve hours apart (the first should be administered in the evening of day one of the cycle) Serious toxicity has occurred where the total daily dose has been given twice a day.

- It must be made clear to all staff, including those in the community, that this is a short course of oral chemotherapy that must not be continued.

References

1. Cunningham D, Starling N, Rao S et al. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. N Engl J Med 2008: 358 (1): 36-46.

REGIMEN SUMMARY

Day One

1. Dexamethasone 8mg oral or intravenous

2. Ondansetron 8mg oral or intravenous

3. Furosemide 40mg oral or intravenous

4. Epirubicin 50mg/m^2 intravenous bolus over 10 minutes

5. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

6. Cisplatin 60mg/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)

7. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

Take Home Medicines

8. Capecitabine 625mg/m^2 twice a day oral for 21 days

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

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

11. Ondansetron 8mg twice a day oral for 3 days 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 statement updated Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.1	July 2014	Header changed Toxicities removed Tabulation throughout < and > written in full NCI-CTC added Renal recommendations updated for cisplatin Administration routes clarified Epirubicin administration changed to 10 minutes Metoclopramide dose changed to 10mg Twice a day used throughout Pyridoxine removed from supportive treatments Mouthwashes updated TTOs clarified Disclaimer added	Dr Debbie Wright Pharmacist	Donna Kimber Pharmacy Technician
1	Aug 2010	None	Dr Debbie 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.