Chemotherapy Protocol

NEUROENDOCRINE

CAPECITABINE-STREPTOZOCIN

Regimen

- Neuroendocrine – Capecitabine-Streptozocin

Indication

- Metastatic or locally advance neuroendocrine tumours irrespective of primary site, predominantly pancreas but also bowel and lung.
- Palliative intent
- WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Capecitabine	Palmar-plantar erythrodysesthesia, diarrhoea, chest pain, mucositis
Streptozocin	Nephrotoxicity, transient increases in LFTs, altered glucose tolerance, hypoglycaemia, confusion, depression

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

Monitoring

Drug

- FBC, LFTs (including albumin) and U&Es prior to each cycle
- EDTA or calculated creatinine clearance prior to each cycle
- Regular monitoring of blood glucose levels
- Urinalysis for signs of proteinuria and glycosuria 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 and drug specific toxicities 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.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent.

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

Neutrophils ($x10^9$/L)	**Platelets ($x10^9$/L)**	**Dose Modifications (capecitabine and streptozocin)**
Greater than or equal to 1	Greater than or equal to 100	100%
Less than 1 or febrile neutropenia	Less than 100 or active haemorrhage	**First occurrence** – delay treatment for 7 days. If counts recover continue with 100% capecitabine dose and 80% streptozocin dose **Second occurrence** – delay for 7 days. If counts recover continue with 80% of the original dose for both agents **Third occurrence** – delay for 7 days. If counts recover continue with the capecitabine at 80% of the original dose and streptozocin at 60% of the original dose

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

Drug	**Dose prior to Starting Treatment**
Capecitabine	There is a lack of information available. In patients with mild to moderate hepatic dysfunction due to liver metastases, 100% of the dose is probably acceptable
Streptozocin	Consider dose modification

The following dose modifications are recommended when hepatic toxicity is encountered following initiation of treatment:

First appearance **NCI Common Toxicity Criteria (CTC) Grade**	**Action**
Grade 2 or less ALT 3.0 - 5.0xULN AST 3.0 – 5.0xULN Bilirubin 1.5 – 3xULN	Delay until grade 1 or below ALT 3xULN or less AST 3xULN or less Bilirubin 1.5xULN o less then restart both drugs at 100% doses
Grade 3 ALT 5 – 20.0xULN AST 5 – 20.0xULN Bilirubin 3.0 – 10xULN	Delay until grade 1 or less, then retreat at; 100% capecitabine dose **and** 80% streptozocin dose

Second appearance **NCI CTC Common Toxicity Criteria Grade**	**Action**
Grade 2 or below ALT 3 - 5xULN AST 3 – 5xULN Bilirubin 1.5 – 3xULN	Delay until grade 1 or below then restart at 100% doses of both drugs
Grade 3 ALT 5 – 20xULN AST 5 – 20xULN Bilirubin 3 – 10xULN	Delay until grade 1 or below, then retreat at; 80% capecitabine dose **and** 80% streptozocin dose

Renal Impairment

Creatinine Clearance (ml/min)	**Dose of capecitabine and streptozocin (% of original dose)**
61 or more	100%
40 - 60	80%
30-39	60%
29 or below	Discontinue

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.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent should then be reduced to 80% of the original dose or discontinued as appropriate.

Capecitabine

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. If chest pain occurs consider stopping capecitabine.

Severe diarrhoea and/or severe mucositis early in the first treatment cycle can be the first presenting toxicity due to DPD enzyme deficiency, in which case potentially fatal neutropenia can quickly follow.

In general when a dose of capecitabine has been reduced it should not be increased at a later date. In addition when capecitabine is stopped for toxicity the doses are omitted, not delayed.

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 at 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 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 grade 0-1.

Streptozocin

In up to 20% of patients, there may be a sudden release of insulin, with hypoglycaemia occurring within 24 hours of treatment. Mild to moderate, reversible abnormalities of glucose tolerance have been reported, therefore, BM's should be monitored during treatment

Regimen

21 day cycle for up to 6 cycles

Drug	Dose	Days	Administration
Capecitabine	625mg/m^2 twice a day	1-21 incl.	Oral
Streptozocin	1000mg/m^2	1	Intravenous infusion in 1000ml sodium chloride 0.9% over 120 minutes

Dose Information

- Capecitabine will be dose banded in accordance with the national dose bands (capecitabine)
- Streptozocin will be dose banded in accordance with the national dose bands (100mg/ml)

Administration Information

Extravasation

- Streptozocin - vesicant

Other

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

Additional Therapy

- Antiemetics

15-30 minutes prior to chemotherapy

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

As take home medication

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

- Mouthcare for the prophylaxis or treatment of mucositis in accordance with CSCCN guidelines.

- Gastric protection with a proton pump inhibitor or a H2 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. Turner N, Strauss S, Sarker D et al. Chemotherapy with 5-fluorouracil, cisplatin and streptozocin for neuroendocrine tumours. Br J Cancer 2010;102:1106-1112.

REGIMEN SUMMARY

Capecitabine-Streptozocin

Day 1

1. Aprepitant 125mg oral
2. Dexamethasone 4mg oral or intravenous bolus
3. Ondansetron 8mg oral or intravenous bolus
4. Streptozocin 1000mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 120 minutes

Take home medicines

5. Capecitabine 625mg/m2 twice a day for 21 days oral
   Administration Instructions
   Start on the evening of day one of the cycle. Take with or after food. Oral SACT
6. Aprepitant 80mg once a day oral for 2 days, starting on day 2 of treatment oral
   Administration Instructions
   Start on day 2 of the cycle
7. Dexamethasone 4mg once a day in the morning for 3 days, starting on day 2 of treatment oral
   Administration Instructions
   Take in the morning with or after food. Start on day 2 of the cycle
8. Metoclopramide 10mg three times a day oral as necessary
   Administration Instructions
   Please supply an original pack as appropriate
9. Ondansetron 8mg twice a day oral for 3 days, starting on the evening of day 1 of treatment
   Administration Instructions
   Start on the evening of day one of the cycle.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	Nov 2020	Updated monitoring with DPD testing Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1	Aug 2019	None	Dr Deborah Wright Pharmacist	Dr Judith Cave Consultant Medical Oncologist Dr Luke Nolan 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 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.