Chemotherapy Protocol

HEAD AND NECK CANCER

CAPECITABINE-CARBOPLATIN (AUC5)-CETUXIMAB

Regimen

- Head and Neck Cancer – Capecitabine-Carboplatin-Cetuximab

Indication

- The treatment of advanced head and neck cancer that has not been previously treated with cetuximab
- WHO performance status 0, 1

Toxicity

Drug	Adverse Effect
Capecitabine	Palmar-plantar erythrodysesthesia, diarrhoea, mucositis, chest pain
Carboplatin	Neuropathy, hypersensitivity
Cetuximab	Infusion related reactions, interstitial lung disease, skin reactions, electrolyte abnormalities, fatigue, abdominal pain, constipation

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

Monitoring

Regimen

- FBC, LFT's and U&E's prior to day one of treatment
- Monitor for hypersensitivity reactions for 60 minutes after the end of the cetuximab infusion
- 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

There is little need to adjust the dose of cetuximab for haematological toxicity. The following applies to capecitabine and carboplatin only.

On day one if the neutrophils are less than $1.5x10^9$/L in the first instance delay treatment for 7 days. If counts recover at this point continue at the initial dose. If counts remain low continue with treatment using a 20% dose reduction. If the myelosuppression recurs despite this dose reduction stop treatment.

On day one if the platelets are less than $100x10^9$/L in the first instance delay treatment for 7 days. If the counts recover at this point continue at the initial dose. If the counts still fall within this range continue using a 20% dose reduction. If the platelet level falls below $50x10^9$/L reduce the dose by 50%.

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)
Capecitabine	There is little published information available. No dose reductions are necessary for those with mild to moderate hepatic dysfunction due to liver metastasis
Carboplatin	No adjustment necessary
Cetuximab	Administer only when the transaminases are 5xULN or below and the bilirubin is 1.5xULN or below

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
Carboplatin	Less than 20	Do not use
	Changes in the GFR of more than 10% between cycles may require dose adjustment	
Cetuximab	If the creatinine is more than 180 (1.5xULN), do not use	

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.

If any NCI-CTC grade 1toxicity 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.

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 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 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.

Consider stopping capecitabine therapy if chest pain occurs.

Cetuximab

Allergic or hypersensitivity reactions have occurred during the administration of cetuximab. For a NCI-CTC grade 1 reaction reduce the infusion rate by 50%. For a NCI-CTC grade 2 reaction, stop the infusion and administer supportive therapies as indicated. When the reaction has resolved to NCI-CTC grade 1 or below resume the infusion at 50% of the previous rate. For a NCI-CTC grade 3 or 4 toxicity stop the infusion immediately and disconnect the tubing from the patient. Administer appropriate supportive therapies. Once recovered, patients should not receive cetuximab again. Once the rate has been reduced it should not be increased on subsequent infusions.

If a second reaction occurs on the slower infusion rate the infusion should be stopped and no further treatment given.

An acneiform skin rash occurs in over 70% of those receiving cetuximab. The onset is normally within three weeks of starting therapy and often resolves after week twelve. For a NCI-CTC grade 1-2 reaction use symptomatic treatments such as topical or oral antibiotics and continue with the cetuximab. For a NCI-CTC grade 3 toxicity delay treatment until the toxicity resolves to NCI-CTC grade 2 or below. If this occurs within fourteen days resume cetuximab at the same dose. If more than fourteen days is required stop treatment. If the NCI-CTC grade 3 toxicity occurs for a second and third time the cetuximab may again be delayed for up to and including fourteen days with concomitant dose reductions to 200mg/m^2 and 150mg/m^2 respectively. Cetuximab dose reductions are permanent. The cetuximab must be discontinued if more than two consecutive infusions are withheld or a fourth episode of a NCI-CTC grade 3 skin toxicity develops or a NCI-CTC grade 4 toxicity at any time.

UV radiation may worsen skin reactions. Sun safety practices should be followed during and for up to two months after the end of treatment.

Stop treatment if there is a confirmed pneumonitis.

Regimen

The starting dose of carboplatin AUC5 is used with calculated GFR. AUC4 may be considered with EDTA clearance, seek advice from the appropriate consultant before prescribing. The recommended maximum dose when using a calculated creatinine clearance at AUC5 is 750mg. If you have an obese patient or an individual with a calculated creatinine clearance above 125ml/min please seek advice from the relevant consultant.

Consider a dose reduction in poor performance patients.

It should be noted that the dose of carboplatin may need to be altered if there is a change (improvement or reduction) in renal function of more than 10% from the previous cycle.

21 day cycle for 6 cycles

The starting dose of carboplatin AUC 5 is used with calculated GFR. AUC 4 may be considered with EDTA clearance, seek advice from the appropriate consultant before prescribing. The recommended maximum dose when using a calculated creatinine clearance at AUC5 is 750mg (creatinine clearance 125ml/min). This is not a dose included in the national dose banding table. The maximum dose has been set at 790mg in ARIA. Please check if this dose is appropriate. If you have an obese patient or an individual with a calculated creatinine clearance above 125ml/min please seek advice from the relevant consultant.

It should be noted that the dose of carboplatin may need to be altered if there is a change (improvement or reduction) in renal function of more than 10% from the previous cycle.

The cetuximab may be continued if the disease is at least stable at the end of six cycles until disease progression or toxicity occurs.

Cycle One

Drug	Dose	Days	Route
Capecitabine	1000mg/m^2 twice a day	1-10 incl	Oral
Carboplatin	AUC5 (max dose)	1	Intravenous infusion in 500ml glucose 5% over 60 minutes
Cetuximab	400mg/m^2	1	Intravenous infusion (see administration)
Cetuximab	250mg/m^2	8, 15	Intravenous infusion (see administration)

Cycle Two Onwards

Drug	Dose	Days	Route
Capecitabine	1000mg/m^2 twice a day	1-10 incl	Oral
Carboplatin	AUC5 (max dose)	1	Intravenous infusion in 500ml glucose 5% over 60 minutes
Cetuximab	250mg/m^2	1, 8, 15	Intravenous infusion (see administration)

Dose Information

- Capecitabine will be dose banded in accordance with the national dose bands
- Carboplatin will be dose banded in accordance with the national dose bands (10mg/ml)

- The maximum dose of carboplatin for AUC 5 is 750mg. This will be set as 790mg in ARIA to comply with national dose bands.

- It should be noted that the dose of carboplatin may need to be altered if there is a change (improvement or reduction) in renal function of more than 10% from the previous cycle.

- Cetuximab will be dose banded in accordance with the national dose bands (5mg/ml)

Administration Information

Extravasation

- Carboplatin - irritant

- Cetuximab - neutral

Other

- Capecitabine should start on the evening of day 1

- Capecitabine should be taken with or after food

- Individuals should be monitored for hypersensitivity reactions for sixty minutes after finishing the cetuximab infusion. Do not administer other chemotherapy during this period.

- The rate of administration of cetuximab must not exceed 5mg/min for the first infusion (minimum 120 minutes). If well tolerated subsequent infusions may be given at a rate of 10mg/min (minimum 60 minutes).

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy on **day one** only;

  - dexamethasone 8mg oral or intravenous or equivalent dose
  - ondansetron 8mg oral or intravenous

  As take home medication;

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

- 30 minutes prior to cetuximab infusion;
  - chlorphenamine 10mg intravenous
  - dexamethasone 8mg oral or intravenous (given as part of antiemetic regimen on day 1)
  - H_2 antagonist according to local formulary choice and availability
  - 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 according to local or national policy on 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. Vermorken JB, Mesia R, Rivera F et al. Platinum based chemotherapy plus cetuximab in head and neck cancer. N Engl Med 2008; 359 (11): 1116-1126.

REGIMEN SUMMARY

Capecitabine-Carboplatin(AUC5)-Cetuximab

Day One Cycle One

1. Chlorphenamine 10mg intravenous

2. Dexamethasone 8mg oral or intravenous or equivalent dose

3. Paracetamol 1000mg oral
   Administration Instructions
   Please check if the patient has taken paracetamol. The maximum dose is 4000mg in every 24 hours

4. H_2 antagonist according to local formulary choice and availability
   Administration Instructions:
   Administer according to local formulary choice and availability one of the following 30 minutes prior to SACT;
   - famotidine 20mg oral once only
   - nizatidine 150mg oral once only
   - ranitidine 150mg oral once only
   - ranitidine 50mg intravenous once only

If there is no stock of these products due to national shortages treatment may proceed without the H_2 antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H_2 antagonist treatment.

All infusion related reactions must be recorded in the ARIA journal and reported to the appropriate consultant. Many Trusts do not administer an H_2 antagonist from cycle three onwards. They have been left in the ARIA protocols so that decisions can be made on an individual Trust and patient basis.

5. Cetuximab 400mg/m^2 intravenous infusion

An interval of 60 minutes should be left between administration of cetuximab and carboplatin

6. Ondansetron 8mg oral or intravenous
   Administration Instructions
   Administer 15-30 minutes prior to SACT. This may be given as ondansetron 8mg intravenous if required

7. Warning - Carboplatin Maximum Dose
   Administration Instructions
   The dose of carboplatin is capped at a creatinine clearance of 125ml/min. The internationally recommended maximum dose of carboplatin for AUC 5 is 750mg. The national dose bands do not contain this dose so the cap has been set at 790mg in ARIA. Please check this dose is appropriate for your patient.

8. Carboplatin AUC 5 intravenous infusion in 500ml glucose 5% over 60 minutes
   Administration Instructions
   The dose of carboplatin is capped at a creatinine clearance of 125ml/min. The internationally recommended maximum dose of carboplatin for AUC 5 is 750mg. The national dose bands do not contain this dose so the cap has been set at 790mg in ARIA. Please check this dose is appropriate for your patient

Take Home Medicines (day 1 only)

9. Capecitabine 1000mg/m^2 twice a day for 10 days starting on the evening of day one of the cycle oral
   Administration Instructions
   Oral SACT
   Start on the evening of day 1 of the cycle

10. Dexamethasone 4mg twice a day for 3 days oral starting on day two of the cycle
    Administration Instructions
    Take 4mg twice a day (morning and lunch) for 3 days starting on day 2 of the cycle

11. Metoclopramide 10mg three times a day when required oral
Administration Instructions
Please supply 28 tablets or an original pack as appropriate

Day Eight and Fifteen Cycle One

12. Chlorphenamine 10mg intravenous

13. Dexamethasone 8mg oral or intravenous or equivalent dose
Administration Instructions
Administer 15-30 minutes prior to SACT. This may be administered as dexamethasone 8mg intravenous

14. Paracetamol 1000mg oral
Administration Instructions
Please check if the patient has taken paracetamol. The maximum dose is 4000mg in every 24 hours

15. H_2 antagonist according to local formulary choice and availability
Administration Instructions:
Administer according to local formulary choice and availability one of the following 30 minutes prior to SACT;
- famotidine 20mg oral once only
- nizatidine 150mg oral once only
- ranitidine 150mg oral once only
- ranitidine 50mg intravenous once only

If there is no stock of these products due to national shortages treatment may proceed without the H_2 antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H_2 antagonist treatment.

All infusion related reactions must be recorded in the ARIA journal and reported to the appropriate consultant. Many Trusts do not administer an H_2 antagonist from cycle three onwards. They have been left in the ARIA protocols so that decisions can be made on an individual Trust and patient basis.

16. Cetuximab 250mg/m^2 intravenous infusion

Day One Cycle Two Onwards

17. Chlorphenamine 10mg intravenous

18. Dexamethasone 8mg oral or intravenous or equivalent dose
Administration Instructions
Administer 15-30 minutes prior to SACT. This may be administered as dexamethasone 8mg intravenous

19. Paracetamol 1000mg oral
Administration Instructions
Please check if the patient has taken paracetamol. The maximum dose is 4000mg in every 24 hours

20. H_2 antagonist according to local formulary choice and availability
Administration Instructions:
Administer according to local formulary choice and availability one of the following 30 minutes prior to chemotherapy;
- famotidine 20mg oral once only
- nizatidine 150mg oral once only
- ranitidine 150mg oral once only
- ranitidine 50mg intravenous once only

If there is no stock of these products due to national shortages treatment may proceed without the H_2 antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H_2 antagonist treatment.

All infusion related reactions must be recorded in the ARIA journal and reported to the appropriate consultant. Many Trusts do not administer an H_2 antagonist from cycle three onwards. They have been left in the ARIA protocols so that decisions can be made on an individual Trust and patient basis.

21. Cetuximab 250mg/m^2 intravenous infusion

22. Ondansetron 8mg oral or intravenous
Administration Instructions
Administer 15-30 minutes prior to SACT. This may be given as ondansetron 8mg intravenous if required

An interval of 60 minutes should be left between administration of cetuximab and carboplatin

23. Warning - Carboplatin Maximum Dose
Administration Instructions
The dose of carboplatin is capped at a creatinine clearance of 125ml/min. The internationally recommended maximum dose of carboplatin for AUC 5 is 750mg. The national dose bands do not contain this dose so the cap has been set at 790mg in ARIA. Please check this dose is appropriate for your patient.

24. Carboplatin AUC 5 intravenous infusion in 500ml glucose 5% over 60 minutes
Administration Instructions
The dose of carboplatin is capped at a creatinine clearance of 125ml/min. The internationally recommended maximum dose of carboplatin for AUC 5 is 750mg. The national dose bands do not contain this dose so the cap has been set at 790mg in ARIA. Please check this dose is appropriate for your patient

Take Home Medicines

25. Capecitabine 1000mg/m^2 twice a day for 10 days oral
Administration Instructions
Oral SACT
Start on the evening of day 1 of the cycle

26. Dexamethasone 4mg twice a day for 3 days oral starting on day two of the cycle
Administration Instructions
Take 4mg twice a day (morning and lunch) for 3 days starting on day 2 of the cycle

27. Metoclopramide 10mg three times a day when required oral
Administration Instructions
Please supply 28 tablets or an original pack as appropriate

Day Eight and Fifteen Cycle Two Onwards

28. Chlorphenamine 10mg intravenous

29. Dexamethasone 8mg oral or intravenous or equivalent dose
Administration Instructions
Administer 15-30 minutes prior to SACT. This may be administered as dexamethasone 8mg intravenous

30. Paracetamol 1000mg oral
Administration Instructions
Please check if the patient has taken paracetamol. The maximum dose is 4000mg in every 24 hours

31. H_2 antagonist according to local formulary choice and availability
Administration Instructions:
Administer according to local formulary choice and availability one of the following 30 minutes prior to chemotherapy;

- famotidine 20mg oral once only
- nizatidine 150mg oral once only
- ranitidine 150mg oral once only
- ranitidine 50mg intravenous once only

If there is no stock of these products due to national shortages treatment may proceed without the H_2 antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H_2 antagonist treatment.

All infusion related reactions must be recorded in the ARIA journal and reported to the appropriate consultant. Many Trusts do not administer an H_2 antagonist from cycle three onwards. They have been left in the ARIA protocols so that decisions can be made on an individual Trust and patient basis.

32. Cetuximab 250mg/m^2 intravenous infusion

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Aug 2022	Carboplatin national dose bands added Administration instructions added in summary Warning added in summary	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	Nov 2020	Update of premedication due to shortage of IV ranitidine. IV ranitidine changed to H_2 antagonist according to local formulary choice and availability Coding removed Dose banding statement updated Monitoring updated with DPD testing Carboplatin max dose added Paracetamol admin instructions updated	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1	Dec 2014	None	Dr Debbie Wright Pharmacist	Dr S Ramkumar Consultant Clinical 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 Hospital 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.