Chemotherapy Protocol

GASTROINTESTINAL (UPPER) CANCER

CARBOPLATIN (AUC2)-PACLITAXEL-RADIOTHERAPY

Regimen

- Gastrointestinal (Upper) Cancer – Carboplatin(AUC2)-Paclitaxel-Radiotherapy

Indication

- Neoadjuvant treatment of resectable cancer of the oesophagus or oesophagogastric junction
- WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Carboplatin	Thrombocytopenia, peripheral neuropathy, nephrotoxicity at high doses, electrolyte disturbances
Paclitaxel	Hypersensitivity, hypotension, bradycardia, peripheral neuropathy, myalgia and back pain on administration

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

Monitoring

Drugs

- FBC, LFTs and U&Es prior to each day of treatment
- EDTA or calculated creatinine clearance before each treatment

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)	**Dose Modifications (carboplatin and paclitaxel)**
Greater than or equal to 1	100%
Less than 1	Delay chemotherapy until neutrophils are greater than or equal to $1x10^9$/L then continue with 75% of the original dose for all subsequent doses. Continue radiotherapy during this time.
Platelets ($x10^9$/L)	**Dose Modifications (carboplatin and paclitaxel)**
Greater than or equal to 75	100%
25 - 74	Delay chemotherapy for until platelets are greater than or equal to $75x10^9$/L then continue with 75% of the original dose for all subsequent doses. Continue radiotherapy during this time.
Less than 25	Delay chemotherapy until platelets are greater than or equal to $75x10^9$/L then continue with 75% of the original dose for all subsequent doses. Continue radiotherapy during this time.

Hepatic Impairment

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

Drug	**Bilirubin µmol/L**		**AST/ALT units**	**Dose (% of original dose)**
Carboplatin	N/A		N/A	No dose adjustment needed
Paclitaxel	more than 1.25xULN	and	more than 10xULN	Consider dose adjustment
	more than 51			Not recommended

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Carboplatin*	less than 20	Omit
Paclitaxel	N/A	No dose adjustment needed

* Significant changes in GFR of more than 10% may require dose adjustment.

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 toxicities grade 2 and above, interrupt chemotherapy treatment until the toxicity has resolved to NCI-CTC grade 1 or below and then refer to the table below for dose modifications to be applied to all subsequent doses.

Continue radiotherapy regardless of any delays to chemotherapy treatment.

Dose modifications apply to both carboplatin and paclitaxel.

Incidence	Grade 2	Grade 3	Grade 4
1st occurrence	Resume at original dose	Resume at 75% of original dose	Discontinue treatment
2nd occurrence of same toxicity	Resume at 75% of original dose	Resume at 50% of original dose	N/A
3rd occurrence of same toxicity	Resume at 50% of original dose	Discontinue treatment	N/A
4th occurrence of same toxicity	Discontinue treatment	N/A	N/A

Regimen

35 day cycle for 1 cycle starting on the first or second day of radiotherapy

Drug	Dose	Days	Administration
Carboplatin	AUC 2 (maximum dose 300mg)	1,8,15,22,29	Intravenous infusion in 500ml glucose 5% over 60 minutes
Paclitaxel	50mg/m^2	1,8,15,22,29	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes

Dose Information

- The recommended maximum dose when using a calculated creatinine clearance at AUC2 is 300mg. If you have an obese patient or an individual with a calculated creatinine clearance above 125ml/min please seek advice from the relevant consultant.

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

- Paclitaxel will be dose banded in accordance with the national dose bands (6mg/ml)

Administration Information

Extravasation

- Carboplatin – irritant

- Paclitaxel - vesicant

Other

- Hypersensitivity reactions tend to occur with the first or second infusion of paclitaxel. Paclitaxel infusion should be interrupted for minor symptoms such as flushing or localised rashes. If these resolve promptly (within 5 minutes) the infusion may be restarted at a lower rate with intensive monitoring. Immediately discontinue the infusion for server reactions which include profound hypotension, bronchospasm and generalised erythema.

- Paclitaxel must be administered via a non-PVC administration set containing an in-line 0.22 micron filter.

- Paclitaxel should always be administered prior to carboplatin.

Additional Therapy

- Premedication to reduce of risk of hypersensitivity reaction

  30 minutes before chemotherapy

  - chlorphenamine 10mg intravenous
  - dexamethasone 10mg intravenous, or nearest equivalent dose
  - H_2 antagonist according to local formulary choice and availability

- Antiemetics

  15-30 minutes prior to chemotherapy

  - ondansetron 8mg oral or intravenous

As take home medication

- dexamethasone 4mg once a day oral for 2 days starting the day after chemotherapy
- metoclopramide 10mg three times a day oral as necessary

- 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.

References
1. van Hagen P, Hulshof M, van Lanschot J et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012; 366: 2074-2084.
2. van Heijl M, van Lanschot J, Koppert LB et al. Neoadjuvant chemoradiation followed by surgery versus surgery alone for patients with adenocarcinoma or squamous cell carcinoma of the esophagus (CROSS). BMC Surgery 2008; 8 (21): 1471-1482.
3. van Meerten E, Muller K, Tilanus HW et al. Neoadjuvant concurrent chemoradiation with weekly paclitaxel and carboplatin for patients with oesophageal cancer: a phase II study. Br J Cancer 2006; 94: 1389-1394.

REGIMEN SUMMARY

Carboplatin (AUC2)-Paclitaxel RT

Cycle 1 Day 1

1. Chlorphenamine 10mg intravenous

2. Dexamethasone 8mg intravenous

3. 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

   There are stock shortages of H_2 antagonists. The administration may proceed without these agents being given unless there is a specific instruction from the prescriber in the ARIA journal that a H_2 antagonist must be administered. 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.

4. Ondansetron 8mg oral or intravenous

5. Paclitaxel 50mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
   Administration Instructions
   Paclitaxel must be administered via a non-PVC administration set containing an in-line 0.22 micron filter

6. Carboplatin AUC 2 (maximum dose 300mg) intravenous infusion in 500ml glucose 5% over 60 minutes

Take home medicines

7. Dexamethasone 4mg once a day oral for 2 days starting the day after chemotherapy

8. Metoclopramide 10mg three times a day oral as necessary
   Administration instructions
   Please supply 60 tablets or 2 original packs if appropriate. If further supplies are required on subsequent days please add from the support folder.

Cycle 1 Days 8, 15, 22, 29

9. Chlorphenamine 10mg intravenous

10. Dexamethasone 8mg intravenous

11. 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

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12. Ondansetron 8mg oral or intravenous

13. Paclitaxel 50mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
    Administration Instructions
    Paclitaxel must be administered via a non-PVC administration set containing an in-line 0.22 micron filter

14. Carboplatin AUC 2 (maximum dose 300mg) intravenous infusion in 500ml glucose 5% over 60 minutes

Take home medicines

15. Dexamethasone 4mg once a day oral for 2 days starting the day after chemotherapy

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	October 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	Arum Shortland Pharmacist	Dr Deborah Wright Pharmacist
1.1	Aug 2018	Maximum dose of 300mg added to summary Dose rounding changed to national dose bands Dexamethasone changed to 8mg Disclaimer updated	Dr Deborah Wright Pharmacist	Dr Andrew Bateman Consultant Clinical Oncologist
1	Nov 2014	None	Dr Deborah Wright Pharmacist	Dr Andrew Bateman 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 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 that occur as a result of following these guidelines. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.