

CAPOX (XELOX) Capecitabine & Oxaliplatin)

DRUG ADMINISTRATION SCHEDULE

| Day | Drug | Dose | Route | Diluent & Rate |
|--------------|---------------------|---|----------------------------------|--------------------------------|
| Day 1 | Glucose 5% | 500ml | Infusion | Fast Running / Line Flush |
| | Ondansetron | 8mg | Oral /Slow bolus/15 min infusion | |
| | Dexamethasone | 8mg | IV bolus | Via glucose drip |
| | Oxaliplatin | 130mg/m² | IV Infusion | 500mls Glucose 5% over 2 hours |
| Days 1 to 14 | Capecitabine | 1000mg/m² twice a day | Oral | N/A |

*Ondansetron IV must be infused over 15 minutes in patients over 65 years of age.

DOSE FORM: Capecitabine available as 500mg and 150mg tablets.

CYCLE LENGTH AND NUMBER OF DAYS

Treatment administered every 21 days.

Given for 4 cycles for low-risk Dukes C (T1-3 N1) adjuvant colon cancer, or 8 cycles in high-risk Dukes C (T4 or N2)

Usually given for 4 to 8 cycles for first-line advanced or metastatic disease.

APPROVED INDICATIONS

Treatment of Adjuvant and Advanced Colorectal Cancer, in patients who would otherwise be considered for Oxaliplatin-MdG (FOLFOX).

ELIGIBILITY CRITERIA

Colorectal cancer patients with adequate renal function.

EXCLUSION CRITERIA

Patients with baseline renal function less than 30 ml/min.

Patients incapable of managing oral chemotherapy themselves or with the assistance of a carer

Patients with swallowing difficulties

PREMEDICATION

As above

RECOMMENDED TAKE HOME MEDICATION

Ondansetron 8mg twice daily for 2 days

Dexamethasone 4mg twice daily for 1 to 2 days

Metoclopramide 10 mg three times daily as required

Suggested antiemetic regimen - may vary with local practice. See CINV policy for more details

INVESTIGATIONS / MONITORING REQUIRED

FBC, U&E's, LFT's and tumour markers as appropriate prior to each course of chemotherapy

FBC on the day of chemotherapy

Where CEA is elevated this should be measured before each cycle.

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ASSESSMENT OF RESPONSE

Assessed radiologically after 4th cycle.

Metastatic: Tumour size and patient symptomatic response

Adjuvant There will be no visible disease to monitor for adjuvant treatment.

REVIEW BY CLINICIAN

To be reviewed by either a Nurse, Pharmacist or Clinician before every cycle.

NURSE / PHARMACIST LED REVIEW

On cycles where not seen by clinician.

ADMINISTRATION NOTES

- If diarrhoea is a problem, give loperamide 2 to 4 mg four times daily when required or codeine phosphate.
- **Oxaliplatin is incompatible with saline.** Must use 5% dextrose as diluent and line flush
- Bronchospasm can occur. *If severe laryngeal spasm occurs consider increasing oxaliplatin infusion to 6 hours
- Capecitabine should start on the evening of day 1 and continue until the morning of day 15.
- Capecitabine should be omitted if Grade II toxicity occurs. It can recommence (see Dose Reductions) if toxicity resolves, however the treatment should still stop on day 15. (i.e. Doses are omitted not delayed).
- Note: Grade II Toxicity includes: Diarrhoea defined as an increase of 4-6 stools per day or nocturnal stools.

Laryngo-Pharyngeal Dysesthesia

As with all platinum based chemotherapy, patients may experience allergic reaction during administration. The following table is intended to help differentiate between Platinum Hypersensitivity and Laryngo-pharyngeal Dysesthesia.

| Clinical Symptoms | Laryngo-pharyngeal Dysesthesia | Platinum Hypersensitivity |
|---------------------------|---|--|
| Dyspnoea | Present | Present |
| Bronchospasm | Absent | Present |
| Laryngospasm | Absent | Present |
| Anxiety | Present | Present |
| O ₂ saturation | Normal | Decreased |
| Difficulty swallowing | Present (loss of sensation) | Absent |
| Pruritus | Absent | Present |
| Cold induced symptoms | Yes | No |
| Blood Pressure | Normal or Increased | Normal or Decreased |
| Treatment | Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion | Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate |

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Platinum Hypersensitivity

Patients who have previously experienced Grade I or II Platinum Hypersensitivity should be pre-medicated as below:

45 minutes prior to Oxaliplatin

- Dexamethasone 20 mg IV in 50 mL NS over 15 minutes (or Hydrocortisone 100mg)

30 minutes prior to Oxaliplatin

- Chlorphenamine 10 mg IV and Ranitidine 50 mg IV in 50 mL NS over 20 minutes

EXTRAVASATION See NCA / local Policy

TOXICITIES

- Peripheral neurotoxicity is the main dose limiting toxicity with Oxaliplatin
- Nausea and Vomiting
- Diarrhoea
- Stomatitis
- Palmar/Plantar Erythrodysesthesia (PPE) - can be severe, patients must be forewarned
- Abdominal pain
- Pyrexia, fatigue, asthenia, anorexia
- Myelosuppression
- Hyperbilirubinemia
- Laryngopharyngeal dysaesthesia
- Cardiotoxicity - Occasionally patients may experience coronary artery spasm. Stop Treatment with fluoropyrimidine therapy if this occurs.

Contra-indicated in patients with severe hepatic impairment, a history of severe and unexpected reactions to fluoropyrimidine therapy, hypersensitivity. Avoid concomitant use with allopurinol

DPD Deficiency and Severe Toxicity Risk

Dihydropyrimidine dehydrogenase (DPD) plays an important role in the metabolism of fluoropyrimidine drugs 5-fluorouracil (5FU) and capecitabine. Patients with DPD deficiency may be predisposed to experience increased or severe toxicity when receiving 5-FU or capecitabine, and in some cases these events can be fatal.

For all patients having capecitabine or fluorouracil, the risk of severe side effects from capecitabine or 5FU if patients have a deficiency of DPD must be mentioned and patient given a copy of the DPD toxicity information leaflet from cancer research UK.

Available at <http://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/chemotherapy/side-effects/dpd-deficiency-and-fluorouracil>

DOSE MODIFICATION / TREATMENT DELAYS

Haematological toxicity:

- Delay 1 week if ANC < 1.0 and Platelets < 75
- If delay > 1 week patient will need a 25% dose reduction of Oxaliplatin and Capecitabine
- No dose reduction for CTC grade I/II ANC
- Grade III/IV ANC → delay chemotherapy until recovered, then proceed at 25% capecitabine and oxaliplatin dose reduction
- If further delay(s) for bone marrow suppression occur despite a 25% dose reduction, consider a further 25% dose reduction

Non-haematological toxicities

Hepatic impairment

- Administration of CAPOX should be interrupted if treatment-related elevations in bilirubin of > 2 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of > 2.5 x ULN occur.
- Treatment may be resumed when bilirubin decreases to ≤ 2.0 x ULN or hepatic aminotransferases decrease to ≤ 2.5 x ULN.

Renal function

| GFR | Capecitabine | Oxaliplatin |
|--------------|--------------------|--------------------|
| 30-50 ml/min | 25% dose reduction | No action |
| < 30 ml/min | Contact prescriber | Contact prescriber |

Neurotoxicity:

- Cold related paraesthesia of hands/feet or dysaesthesia/laryngeal spasm syndrome lasting a few hours does not require treatment or dose reduction.
- If severe laryngeal spasm occurs, increase oxaliplatin infusion duration to 6 hours
- If symptoms persist for 14 days and/or there is pain, functional loss, omit oxaliplatin and continue with capecitabine until recovered, then restart oxaliplatin at 25% dose reduction.

Diarrhoea

| | |
|---------------------------------------|--|
| Grade 1 (watery stool 2-3 times/day) | Loperamide 4mg then 2mg QDS PRN. |
| Grade 2 (watery stool 4-6 times/day) | Delay treatment until recovered and give full dose |
| Grade 3/4 (watery stool >7 times/day) | Delay until recovered and resume treatment at 25% reduced dose of oxaliplatin and capecitabine |

Table of PPE (hand/foot syndrome) toxicity grading for capecitabine only

| Grade | Clinical | Functional | Management |
|-------|---|---|---|
| 1 | Numbness, dysesthesia/parathesia, | Discomfort but no interruption of normal activities | |
| 2 | Painful erythema with swelling | Discomfort which affects activities of daily living | Interrupt treatment until grade ≤1 |
| 3 | Moist desquamation, ulceration, Blistering, severe pain | Severe discomfort, unable to work or perform activities of daily living | Interrupt treatment until grade ≤1 and reduce dose by 25% |

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Table of dose adjustments according to CTC toxicity (Not PPE/hand/foot syndrome)

| | Grade 2 | Grade 3 | Grade 4 |
|----------------------------|---|--|-----------------------|
| 1 st appearance | Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible | Interrupt treatment until resolved to grade 0/1, then continue at 75% of original dose with prophylaxis where possible | Discontinue treatment |
| 2 nd appearance | Interrupt treatment until resolved to grade 0/1, then continue at 75% of original dose | Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose | |
| 3 rd appearance | Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose | Discontinue treatment | |
| 4 th appearance | Discontinue treatment | | |

Once the capecitabine dose has been reduced, it should **not** be increased at a later time. Omitted doses are **not replaced or restored**, instead the patient should resume the planned treatment cycle.

TREATMENT LOCATION

Can be given at Cancer Centre or Cancer Unit

REFERENCES:

1. FOCUS2 Trial Protocol. August 2003 (version 1.1)
2. BCCA Protocol Summary for ADJUVANT Combination Chemotherapy for Stage III Colon Cancer Using Oxaliplatin, 5-Fluorouracil and Folinic Acid (Leucovorin). Reference: UGIAJFFOX. Mar 2006
3. Cassidy J et al (2004) XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. J Clin Oncol. 2004 Jun 1;22(11):2084-91.
4. Shi Q, Sobrero AF, Shields AF et al, Prospective pooled analysis of six phase III trials investigating duration of adjuvant (adjuv) oxaliplatin-based therapy (3 vs 6 months) for patients (pts) with stage III colon cancer (CC): The IDEA (International Duration Evaluation of Adjuvant chemotherapy) collaboration J. Clin. Oncol. 35, (suppl; abstr LBA1) (2017).

Document Control

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|---------------------------|--|---|----------|
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| Summary of Changes | 1.1 | Reformatted from old NCN/CCA versions | |
| | 1.2 | Updated capecitabine dose/ toxicity modification advice | |
| | 1.3 | Protocol reviewed | |
| | 1.4 | Protocol reviewed and reissued, Antiemetic advice updated | |
| | 1.5 | Protocol reviewed. DPD warning added. | |