# CAPOX- Capecitabine and Oxaliplatin (colorectal)

## Indication

Neo-adjuvant chemotherapy as part of TNT (total neoadjuvant therapy) for rectal cancer.

Biopsy proven adenocarcinoma of the rectum with one or more high risk features (T4a/b, extramural vascular invasion, N2, involved/threatened mesorectal fascia, enlarged lateral pelvic lymph nodes).

Patients initially receive pelvic radiotherapy 25Gy in 5 fractions. TNT chemotherapy regime should commence 11-18 days following completion of radiotherapy.

Surgery is usually planned for 2-4 weeks after completing 18 weeks of chemotherapy.

Neoadjuvant chemotherapy for colorectal cancer

Adjuvant chemotherapy for colorectal cancer

Metastatic colorectal cancer

## ICD-10 codes

Codes prefixed with C20

## Regimen details

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1 | Oxaliplatin | 130mg/ $m^2$ | IV infusion |
| 1-14 | Capecitabine | 1000mg/$m^2$ BD | PO |

## Cycle frequency

21 days

## Number of cycles

TNT: 6 cycles
Neo-adjuvant: 4 cycles
Adjuvant: 4- 8 cycles
Metastatic: treat until disease progression

## Administration

Oxaliplatin is administered in 500ml of 5% glucose over 2 hours. Oxaliplatin is not compatible with sodium chloride 0.9%. Lines must not be pig-backed or flushed with sodium chloride 0.9% immediately after the infusion.

Patients should be observed closely for platinum hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the

initiation of the infusion of oxaliplatin. Facilities for the treatment of hypotension and bronchospasm must be available.
If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require discontinuation of therapy: the infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Chlorpheniramine 10mg IV may be administered.
Severe reactions such as hypotension, bronchospasm or generalized rash/erythema require immediate discontinuation of oxaliplatin, and appropriate therapy should be initiated.

Oxaliplatin may cause transient paraesthesia of hands and feet and laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patients should be well advised on precautions to be taken. This does not require treatment or dose reduction, but subsequent infusions should be given over 6 hours.

Capecitabine is available as 150mg and 500mg tablets
Tablets should be taken after food and swallowed whole with a glass of water.

## Pre-medication

Antiemetics as per local policy
Patient who have previously experienced Grade 1 or Grade 2 platinum hypersensitivity should receive the following pre-medication:

- 30 minutes prior to oxaliplatin: Dexamethasone 20mg IV
- 30 minutes prior to oxaliplatin: Chlorpheniramine 10mg IV and Ranitidine 50mg IV

## Emetogenicity

This regimen has a moderate- high emetogenic potential

## Additional supportive medication

Mouthwashes as per local policy. Loperamide if required.
Metoclopramide 10mg tds prn.

## Extravasation

Oxaliplatin is an exfoliant (Group 4).

## Investigations – pre first cycle

| Investigation | Validity period |
|---|---|
| FBC | 14 days |
| U+E (including creatinine) | 14 days |
| LFTs (including AST) | 14 days |
| Calcium | 14 days |
| Magnesium | 14 days |
| CEA | 14 days |
| DPYD mutation testing | none |
| Hepatitis B serology (HBsAG, HBcAb) | none |
| HbA1c | 3 months |
| Random glucose | 14 days |

## Investigations - pre subsequent cycles

FBC, U&E (including creatinine), LFT (including AST), calcium, magnesium, random glucose, CEA

## Standard limits for administration to go ahead

If blood results not within range, authorisation to administer must be given by prescriber/ consultant.

| **Investigation** | **Limit** |
|---|---|
| Neutrophils | ≥ 1.5 x $10^9$/L (discuss with consultant ≥ 1.0- <1.5) |
| Platelets | ≥ 75 x $10^9$/L |
| Bilirubin | < 1.5 x ULN |
| AST/ALT | < 2.5 x ULN |
| Creatinine Clearance (CrCl) | ≥ 50mL/min |

## Dose modifications

- **Haematological toxicity**

Defer treatment for 1 weeks if neutrophil count <1.0 x $10^9$/L and/or platelets <75 x $10^9$/L and delay next cycle until recovery. Recommence with dose modifications as below:

| Neutrophils | Platelets | Oxaliplatin dose | Capecitabine dose |
|---|---|---|---|
| ≥1.0 and | ≥75 | 100% | 100% |
| 0.5-0.9 or | 50-74 | 100mg/$m^2$ | 100% |
| <0.5 and/or | 25-49 | 100mg/$m^2$ | 100% |
| <0.5 and/or | <25 | 65mg/$m^2$ | 100% |

If febrile neutropenia (neutrophils<0.5 x $10^9$/L and fever requiring IV antibiotics)- reduce all subsequent doses of oxaliplatin to 100mg/$m^2$

- **Renal impairment**

| **CrCl** (mL/min) | **Oxaliplatin dose** | **Capecitabine dose** |
|---|---|---|
| ≥ 50 | 100% | 100% |
| 30-49 | 75% | 75% |
| <30 | Omit | Contraindicated |

- **Hepatic impairment**

**Capecitabine:**

Lack of information available. In patients with mild to moderate hepatic dysfunction (bilirubin <3 x ULN and/or AST/ALT <5 x ULN) probably no dose reduction necessary, consultant decision.

**Oxaliplatin:**

Little information available. Probably no dose reduction necessary, consultant decision.
Note that significantly impaired hepatic function may be a sign of disease progression and require cessation of, or change in, treatment.

- **DPYD variants**

All patients due to receive fluoro-pyrimidine based therapy should have a DPD test prior to starting treatment. Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle).

Any patient who has not had a DPD test should be discussed with the consultant prior to going ahead. Patients with variants should be considered for a dose modification following national advice for recommended dose adjustments.

dpd-testing-ukcb-july-2020-final.pdf (theacp.org.uk)

Where a patient has had significant toxicities but the DPD test has shown none of the variants to be present, a further test can be conducted to test the presence of rarer variants.

- **Other toxicities**

**Capecitabine:**
Other toxicities should be managed by symptomatic treatment and/or dose modification (e. by treatment interruption or undertaking a dose reduction).
Once the dose has been reduced, it should not be increased at a later time.

Dose modifications should be made as per the following table:

| **Toxicity grade** | **1st occurrence** | **2nd occurrence** | **3rd occurrence** | **4th occurrence** |
|---|---|---|---|---|
| 0-1 | 100% | 100% | 100% | 100% |
| 2 | Delay then 100% | Delay then 75% | Delay then 50% | Discontinue |
| 3 | Delay then 75% | Delay then 50% | Discontinue | |
| 4 | Delay then 50% | Discontinue | | |

Any delays should be until the toxicity has resolved to grade 0-1.

**Oxaliplatin:**
**Neurological toxicity:**
Dose related peripheral neuropathy can occur with oxaliplatin. It usually occurs after a cumulative dose of 800mg/$m^2$. It can occur once oxaliplatin is completed.
If neurological symptoms occur, use the following oxaliplatin dose adjustments:

| **Toxicity grade** | **Oxaliplatin** |
|---|---|
| 1 (any duration) or grade 2 longer than 7 days | 100% |
| 2 paraesthesia persisting until next cycle | 100mg/$m^2$ |
| 3 paraesthesia lasting longer than 7 days | 100mg/$m^2$ |
| 3 paraesthesia persisting until next cycle | Discontinue permanently |
| 4 of any duration | Discontinue permanently |

In grade 3 or 4 stomatitis or diarrhea, delay until recovers to ≤ grade 2 then reduce oxaliplatin dose to 100mg/$m^2$.
Patients presenting with diarrhea must be carefully monitored until the symptoms have disappeared as a rapid deterioration can occur.
Any delays should be until toxicity has resolved to grade 0-1

## Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Allergic reactions
Neurotoxicity
Nephrotoxicity
Coronary artery spasm*

*Coronary artery spasm is a recognised complication of capecitabine treatment, although the evidence base regarding aetiology, management and prognosis is not particularly strong.
Should a patient receiving capecitabine present with chest pains, stop the treatment. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, the capecitabine should be permanently discontinued.

- **Other side effects**

Headache
Dizziness
Dysgeusia
Transient cerebellar syndrome
Confusion

## Significant drug interactions – for full details consult product literature/ reference texts

**Warfarin/coumarin anticoagulants:** Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

**Oxaliplatin:**
**Avoid nephrotoxic agents as these may increase toxicity of oxaliplatin**

**Capecitabine:**
**Folinates:** Avoid concomitant use of folinic and folic acid – enhanced toxicity of capecitabine.
**Co-trimoxazole/trimethoprim**: Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.
**Phenytoin and fosphenytoin**: Toxicity has occurred during concomitant therapy- monitor levels regularly
**Sorivudine and its analogues**: Co-administration can cause increased toxicity which may be fatal.
**Allopurinol**: A decrease in capecitabine activity has been shown when taken in combination with allopurinol. Avoid if possible
**Antacids**: the use of antacids with capecitabine can decrease absorption-avoid.

## Additional comments

## Fertility/Contraception

Patients should agree to use an acceptable method of birth control to avoid pregnancy for the duration of treatment and for 6 months afterwards. Breastfeeding should be discontinued during treatment. Oxaliplatin may have an anti-fertility effect

## References


- Colorectal NICE guideline NG151 (updated 15 Dec 2021) accessed 11 May 2022
- Bahadoer R, Dijkstra E et al. Short Courseradiotherapy followed by chemotherapy before total mesorectal excision (TME) versus pre-operative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomized, open-label, phase 3 trial The Lancet 2021 22(1): 29-42
- Summary of Product Characteristics (Oxaliplatin) accessed 11 May 2022 via www.medicines.org.uk
- Summary of Product Characteristics (Capecitabine) accessed 11 May 2022 via www.medicines.org.uk
- Personalised Medicine Approach for Fluoro-pyrimidine-based Therapies. UK Chemotherapy Board July 2020 accessed 11 May 2022 via dpd-testing-ukcb-july-2020-final.pdf (theacp.org.uk)


**THIS PROTOCOL HAS BEEN DIRECTED BY DR WILLIAMSON DESIGNATED LEAD CLINICIAN FOR COLORECTAL CANCER**
**RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE**

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|---|---|
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