# Cetuximab + FOLFIRI for the 1st line Treatment of Metastatic Colorectal Cancer

NHS Northern Cancer Alliance

## DRUG ADMINISTRATION SCHEDULE

| Day | Drug | Daily Dose | Route | Diluent and rate |
|---|---|---|---|---|
| Day 1 | Paracetamol | 1000mg | ORAL | |
| | Hydrocortisone | 100mg | IV Bolus | Slow bolus |
| | Chlorpheniramine | 10mg | IV Bolus | Slow bolus |
| | **Cetuximab** | **500mg/m$^2$** | Intravenous | 500ml Sodium Chloride 0.9% over 2 hours |
| | Glucose 5% | 500ml | Infusion | Fast Running for Line Flush |
| | Ondansetron | 8mg | Oral /Slow bolus/15 min infusion** | |
| | *Atropine** | *0.25mg* | *Subcutaneous Bolus* | As required – see below |
| | Calcium Leucovorin (folinic acid) | 300mg | IV Infusion | 250ml Glucose 5% over 2 hours concurrent with oxaliplatin |
| | **Irinotecan** | **180mg/m$^2$** | **IV Infusion** | 250ml Glucose 5% over 2 hours concurrent with folinic acid |
| | Glucose 5% | 500ml | Infusion | Line Flush |
| | **5 Fluorouracil** | **400 mg/m$^2$** | **IV bolus** | Over 5 minutes |
| | **5 Fluorouracil** | **2400 mg/m$^2$** | **via infusor device** | Sodium Chloride 0.9% over 46 hours |
| Day 3 | Attend ward/ clinic for removal of 5-FU infusor device | | | |

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

### NUMBER OF DAYS PER CYCLE

14 days until disease progression

### PREMEDICATION

- Patients MUST receive pre-medication with a paracetamol, corticosteroid and antihistamine prior to the first cycle of Cetuximab. Administration of paracetamol, corticosteroid and antihistamine is recommended on all other cycles.
- ***If acute cholinergic syndrome appears atropine sulphate 250micrograms should be administered by subcutaneous injection unless clinically contraindicated.**
- The manufacturer recommends the use of prophylactic atropine sulphate with subsequent doses of irinotecan.

### APPROVED INDICATIONS

Cetuximab is recommended, within its marketing authorisation, as an option for previously untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in adults in combination with FOLFOX or FOLFIRI.

### RECOMMENDED TAKE HOME MEDICATION

Ondansetron 8mg twice daily for 2 days
Dexamethasone 4mg twice daily for 1 day
Metoclopramide 10mg three times daily as required
Loperamide as required (4mg after first loose stool and 2mg every 2 hours, to a maximum of 16 (2mg) tablets in 24 hours)
For diarrhoea lasting greater than 24 hours give ciprofloxacin 250mg BD.
*Suggested antiemetic regimen - may vary with local practice. See CINV policy for more details*

## INVESTIGATIONS / MONITORING REQUIRED

*Pre-treatment:* Assessment of renal function, FBC, Cardiac history
*Prior to each cycle*: FBC, U&E's, LFT's, magnesium & tumour markers as appropriate
FBC on the day of treatment
Where CEA is elevated this should be measured before each cycle (no need to await result before proceeding with treatment).

## ASSESMENT OF RESPONSE

Tumour size and patient symptomatic response to be assessed at appropriate intervals. All patients must have radiological assessment of disease no later than 8 weeks after starting Cetuximab must be discontinued if there is evidence of disease progression.

## REVIEW BY CLINICIAN

Before each cycle as appropriate

## NURSE / PHARMACIST LED REVIEW

On cycles where not seen by clinician

## ADMINISTRATION NOTES

- Cetuximab 500mg/m$^2$ can be administered faster than 2 hours provided the infusion rate does not exceed 10mg/min.
- Cetuximab 2 weekly schedule is unlicensed therefore used with prescriber accepting responsibility for any drug reactions.
- Sodium Chloride 0.9% must be used for line flushing with Cetuximab
- Cetuximab (as with all monoclonal antibodies) can cause infusion reactions. Administration must only take place in facilities with resuscitation facilities.
- Pulse, Respiration, Blood Pressure and Temperature must be measured during and 1 hour following infusion
- Patients should be warned that on rare occasions they may experience an infusion reaction several hours after cetuximab
- Management of Cetuximab infusion reactions is outlined in the table below:

| **CTC Grade Allergic / Infusion Related Reaction** | **Action required** |
|---|---|
| **Grade 1** – mild<br><br>(Transient rash during infusion, drug fever < 38°C) | Reduce Cetuximab infusion rate by 50% and monitor for worsening of symptoms. Ensure infusion rate does not exceed 4hours. Use lower rate on all subsequent infusions. |
| **Grade 2** – moderate<br><br>(Rash during infusion, flushing, urticaria, dyspnoea, drug fever ≥ 38°C) | Stop Cetuximab infusion.<br>Resume at 50% of rate once symptoms have resolved or reduced to Grade 1. Continue to monitor closely for worsening of symptoms. Use lower rate on all subsequent infusions. |
| **Grade 3 or 4** – severe or life threatening (Symptomatic bronchospasm, with or without urticaria, parenteral medication indicated, allergy-related oedema, angio-oedema, hypotension, anaphylaxis) | Stop infusion immediately.<br><br>Do not re-treat with Cetuximab. |

**FOLFIRI**

- Irinotecan must only be given in units where clear arrangements are made to manage possible toxicity related out of hour's admissions. Patients must be made aware of the risk of delayed diarrhoea occurring 24 hours after the administration of Irinotecan and at any time before the next cycle. This means supplying information sheets to the patient and if appropriate to their GP.
- Early onset diarrhoea (within the first 24 hours) can be a result of acute cholinergic syndrome and may occur in 9% of patients. Symptoms are short lasting and respond within minutes to administration of atropine (0.25-1mg subcutaneously)
- Delayed diarrhoea must be treated immediately with high dose Loperamide (4mg after first loose stool and 2mgs every 2 hours, to a maximum of 16 (2mg) tablets in 24 hours. Hospitalise if condition not resolved in 48 hours.
- Two forms of Folinic Acid are available. The doses given above refer to 'standard' racemic calcium folinate only. If the pure active enantiomer, calcium levofolinate (Isovorin®) is used the dose will generally be half that of the 'standard' folinate.

**EXTRAVASATION** See Local Guidelines

**TOXICITIES**

- Allergic reaction
- Cardio-pulmonary arrest
- Rash/skin reaction to Cetuximab
- Hypomagnesaemia
- Pulmonary toxicity
- Acute cholinergic syndrome (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation)
- Diarrhoea – Risk of severe delayed diarrhoea – can be life threatening
- Myelosuppression
- Alopecia
- Dizziness during treatment
- Palmar/Plantar Erythrodysesthesia
- Darkening/discoloration of veins
- Cardiotoxicity - Occasionally patients may experience coronary artery spasm

**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

### Haematological Toxicity:

- Cetuximab does not normally cause myelosuppression, but is associated with anaemia in up to 10% of patients
- Delay 1 week if ANC < 1.0 and Platelets < 75.
- If delay > 1 week or delay 2 weeks or greater occurs, reduce the 5FU dose (bolus & infusional) and Irinotecan by 20%. Continue at the reduced dose for subsequent cycles unless other toxicity occurs.
- If further delay(s) for bone marrow suppression occur despite a 20% dose reduction, consider a further 20% dose reduction

### Non-Haematological toxicity

- Diarrhoea grade 2 during course of treatment → delay until recovered and give full dose
- Diarrhoea grade 3/ 4 during a course of treatment → delay until recovered and resume treatment at 20% reduced dose of Irinotecan and 5FU
- Hepatic - bilirubin rising consider 50% chemotherapy dose reduction.
- Omit if bilirubin 3 x ULN
- Renal - rising creatinine and GFR < 30ml/min, consider 50% chemotherapy dose reduction. Cetuximab is not renally excreted

### Cetuximab
### Skin Reactions

| | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|
| **CTC (v2) definition** | Macular or popular eruption/erythema without symptoms | Macular or popular eruption/erythema with pruritis or other symptoms; localised desquamation or other lesions covering <50% of body | Symptomatic generalised erythroderma or macular, popular or vesicular eruption or desquamation covering >50% of body |
| **Action** | Continue | Continue | Delay Cetuximab (continue other chemotherapy) |
| **Treatment** | Topical anti-acne cream (e.g. benzoyl peroxide) for face. Salicylic acid in alcoholic lotion for chest/back | As grade 1 plus menthol in aqueous cream.<br><br>Oral antihistamine and oral tetracycline (for 3 months) | As grade 2 plus saline compresses if required. |

Systemic or topical steroids for treatment of rash are not generally advised. Patients on tetracyclines should be advised to avoid prolonged exposure to the sun.

Topical treatments can have a drying effect on the skin. Care should be taken to avoid aggravating xerosis, especially when acne-like rash is fading or becoming scaly. Switch to moisturising creams instead of alcoholic lotion or gel if this occurs.

| Occurrence of ≥ Grade 3 Toxicity | Cetuximab dose once resolved to ≤ grade 2 |
|---|---|
| First | Resume at full dose |
| Second | 400mg/m$^2$ |
| Third | 300mg/m$^2$ |
| Fourth | Discontinue treatment |

**If skin toxicity has not resolved at Grade 2 or better within 3 weeks, discontinue Cetuximab**

## TREATMENT LOCATION

Cancer Centre or Cancer Unit where there is an Oncologist with a specialisation in Colorectal patients as appropriate.

## REFERENCES:

1. Eric Van Cutsem, et. r al, Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer N Engl J Med 2009; 360:1408-1417; April 2,2009 http://www.nejm.org/doi/full/10.1056/NEJMoa0805019
2. Tabernero, J., Pfeiffer, P. and Cervantes, A., 2008. Administration of cetuximab every 2 weeks in the treatment of metastatic colorectal cancer: an effective, more convenient alternative to weekly administration?. The oncologist, 13(2), pp.113-119.

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| **Summary of Changes** | 1.1 | Protocol reviewed and reissued, Antiemetic advice updated | |
| | 1.2 | Updated with new CDF indication following 12th March changes | |
| | 1.3 | Updated against Chemocare parameters, schedule. Updated with NICE guidance. DPD toxicity advice added | |