FLOT for Perioperative treatment of Gastric Cancer

DRUG ADMINISTRATION SCHEDULE

Day	Drug	Dose	Route	Diluent & Rate
Day 0-2	Dexamethasone	8mg BD	Oral	For 3 days start at one day prior to treatment
Day 1	Sodium Chloride 0.9%	500ml	Infusion	Fast Running for Line Flush
	Ondansetron	8mg	Oral /Slow bolus/15 min infusion	
	Docetaxel	**50mg/m^2**	IV Infusion	250ml Sodium Chloride 0.9% over 1 hour
	Glucose 5%	500ml	Infusion	Line Flush
	Calcium Leucovorin (folinic acid)	300mg or 200mg/m^2* (See Note)	IV Infusion	250ml Glucose 5% over 2 hours concurrent with oxaliplatin
	Oxaliplatin	**85 mg/m^2**	IV Infusion	250ml Glucose 5% over 2 hours concurrent with folinic acid
	Glucose 5%	500ml	Infusion	Line Flush
	5 Fluorouracil	**2600 mg/m^2**	via infusor device	0.9% Sodium Chloride over **24 hours**
Day 2	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.

CYCLE LENGTH AND NUMBER OF DAYS

Every 14 days - usually 4 cycles before and after surgery.

APPROVED INDICATIONS

- For perioperative treatment of gastric cancers

ELIGIBILITY CRITERIA

- ECOG performance status 0-1, Karnofsky performance status >70%, adequate hepatic, renal, marrow and cardiac function

EXCLUSION CRITERIA

Patients with baseline renal function less than 30ml/min

PREMEDICATION

As above

RECOMMENDED TAKE HOME MEDICATION

Ondansetron 8mg twice daily for 2 days
Dexamethasone 4mg twice daily for 3 days starting 24 hours prior to chemotherapy. Note if patient has forgotten to take oral steroids, give 20mg Iv dexamethasone pre-treatment.
Metoclopramide 10mg three times daily as required
Suggested antiemetic regimen - may vary with local practice. See CINV policy for more details

FLOT is expected to carry a risk of febrile neutropenia > 20% so patients must be given GCSF primary prophylaxis. See local Area Team GCSF policy. Daily GCSF is recommended for the majority of patients using the locally agreed schedule below. Pegylated filgrastim is an option for patients unable to self- administer.

Day	Drug	Weight	Dose	Route	Diluent & Rate
3	Biosimilar Filgrastim	<78kg*	300 microg (30 MU)	S/C	ONCE daily for SEVEN days starting TWO days after chemo
		≥78kg*	480 microg (48 MU)		
2	Lipegfilgrastim (Lonquex®) or Pegfilgrastim (Neulasta®)	All	6mg	S/C	Single dose given 24 hours after chemo

INVESTIGATIONS / MONITORING REQUIRED
Pre-treatment: Assessment of renal function, FBC, Cardiac history
Prior to each cycle: FBC, U&E's, LFT's & tumour markers as appropriate
FBC on the day of treatment
Where CEA is elevated this should be measured before each cycle.

ASSESSMENT OF 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
- Before docetaxel is given, make sure the patient has taken oral dexamethasone premedication. Docetaxel has been known to produce hypersensitivity reactions; steroid co-medication will also reduce the risk of fluid retention and skin reactions.
- Facilities to treat anaphylaxis MUST be present when the chemotherapy is given.
- Do not need to stop treatment for minor hypersensitivity e.g. reactions, flushing, localised rash.
- Must be stopped for major reactions, e.g. hypotension, bronchospasm and generalised rash.

- **Oxaliplatin is incompatible with saline**. Must use 5% dextrose as diluent /line flush
- Bronchospasm can occur. * If severe laryngeal spasm occurs consider increasing Oxaliplatin infusion to 6 hours
- Patient requires semi-permanent IV access for this treatment, e.g. PICC line/ Hickman catheter
- Diarrhoea is common, and may require intervention with fluids and electrolytes if severe. If diarrhoea is a problem, give loperamide 2 to 4 mg four times daily as required or codeine phosphate 30mg four times daily and stop 5FU infusion if diarrhoea moderate/severe.
- 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.

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	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

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

- Anaphylaxis and hypersensitivity reactions
- Fluid retention syndrome
- Pain on administration
- Joint pains
- Deranged LFT's
- Peripheral neurotoxicity very common with Oxaliplatin. (dose limiting toxicity)
- Myelosuppression
- Cold induced parathesia
- Nausea and Vomiting
- Allergic reaction
- Diarrhoea
- Stomatitis
- Palmar/Plantar Erythrodysesthesia
- Darkening/discoloration of veins
- Cardiotoxicity - Occasionally patients may experience coronary artery spasm
- Laryngopharyngeal dysesthesia

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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 < 1.5 and/or Platelets < 100
- No dose reduction for CTC grade I/II ANC

Non–Haematological toxicity:

- No dose reduction should apply to oxaliplatin in case of PPE
- In case of Grade III/IV stomatitis or diarrhoea despite a 20% reduction of 5FU, Oxaliplatin should be reduced by 20%

Neurotoxicity:

- Cold related paraesthesia of hands/feet or dyseasthesia/laryngeal spasm syndrome lasts a few hours and should not routinely require treatment or dose reduction.
- If severe laryngeal spasm occurs, consider increasing Oxaliplatin infusion to 6 hours
- If symptoms persist for 14 days and/or there is pain, functional loss, omit Oxaliplatin and continue with 5FU/FA until fully recovered, then restart Oxaliplatin at 20% dose reduction

TREATMENT LOCATION

Can be given at Cancer Centre or Cancer Unit

REFERENCES:

1. Al-Batran SE, Homann N, Schmalemberg H, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): a multicenter, randomized phase 3 trial. J Clin Oncol. 2017;35(suppl; abstr 4004).

Document Control

Document Title:	FLOT for Perioperative treatment of Gastric Cancer		
Document No:	CRP18 UGI018	**Current Version:**	1.0
Reviewer:	Chris Beck, Cancer Alliance Pharmacist	**Date Approved:**	06/09/2018
Approved by:	Steve Williamson, Consultant Pharmacist, Northern Cancer Alliance	**Due for Review:**	06/09/2021
Summary of Changes	1.0	First draft	