Systemic Anti Cancer Treatment Protocol

FLOT
Gastroesophageal Cancer

PROTOCOL REF: MPHAFLOTGA
(Version No: 1.1)

Approved for use in

Neo-adjuvant/adjuvant treatment of gastric and gastroeosophageal junction adenocarcinoma.

Dosage

Drug	Dose	Route	Frequency
Docetaxel	50mg/m^2	IV	Day 1 of 14 day cycle
Oxaliplatin	85mg/m^2	IV	Day 1 of 14 day cycle
Folinic Acid	350mg	IV	Day 1 of 14 day cycle
Fluorouracil	2600mg/m^2	IV	Day 1 of 14 day cycle

8 cycles in total (4 neo-adjuvant, 4 adjuvant)

Supportive Treatments:

Dexamethasone tablets 8mg twice daily for 3 days starting 24 hours before chemotherapy

Domperidone 10mg oral tablets, up to 3 times a day or as required

Loperamide 4mg at onset then 2mg after each loose stool (max.16mg in 24hrs)

Filgrastim s/c on days 5-9 of each cycle

Extravasation risk

Docetaxel

VESICANT – refer to trust / network extravasation policy – specific treatment may apply

Oxaliplatin

EXFOLIANT – use heat and compression, consider hyaluronidase

Fluorouracil

INFLAMMANT - use cold pack and compression

Administration

Day	Drug	Dose	Route	Diluent and rate
0	**Dexamethasone**	**8mg**	**PO**	Twice daily for 3 days starting 24 hours before docetaxel
1	**Ondansetron** 30mins before chemotherapy	**16mg**	**PO**	
	Docetaxel	**50mg/m^2**	**IV**	250mL Sodium Chloride 0.9% infusion over 60 minutes
	Line flush with 5% Glucose			
	Oxaliplatin	**85mg/m^2**	**IV**	500mL Glucose 5% infusion over 2 hours
	Folinic Acid	**350mg**	**IV**	250mL Glucose 5% infusion over 2 hours
	Fluorouracil	**2600mg/m^2**	**IV**	Sodium chloride 0.9% over 24 hours via infusor device

Oxaliplatin and folinic acid should be administered concurrently

Docetaxel hypersensitivity: Reactions may occur within a few minutes following the initiation of treatment with docetaxel, facilities for the treatment of hypotension and bronchospasm should be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised rash with or without pruritus do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate treatment. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.

Platinum hypersensitivity: can cause dyspnoea, bronchospasm itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators.

Grade 1 or 2 hypersensitivity reactions do not require dose modification of oxaliplatin and patients may continue with hypersensitivity premedication:

- 45 minutes prior to Oxaliplatin – dexamethasone 20mg IV in 50mL Sodium Chloride 0.9% over 15 minutes
- 30 minutes prior to Oxaliplatin – chlorphenamine 10mg IV and ranitidine 50mg IV in 50mL Sodium Chloride 0.9% over 20 minutes (compatible up to 3 hours when mixed in bag)

Laryngo-pharyngeal dysaesthesia: characterized by loss of sensation of breathing without any objective evidence of distress (hypoxia, laryngospasm or bronchospasm). May be exacerbated by cold air. If this occurs during the infusion, stop the infusion immediately and observe the patient. Resolution is relatively rapid (within minutes to a few hours). Check oxygen saturation; if normal an anxiolytic agent may be given. The infusion can be restarted at a slower rate at the clinicians' discretion.

For subsequent cycles the duration should be prolonged (4-6 hours).

Clinical Symptoms	Laryngo-pharyngeal Dysaesthesia	Platinum Hypersensitivity
Dyspnoea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O2 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; observe in a clinical setting until symptoms reduce or at clinician's discretion	Oxygen, steroids, adrenaline, bronchodilators; fluids and vasopressors if appropriate

Main Toxicities

Docetaxel
Myelosuppression, hypersensitivity and infusion related, cutaneous reactions and nail changes, fluid retention, alopecia, peripheral neurotoxicity, stomatitis, diarrhoea, ovarian failure/infertility
Oxaliplatin
Nausea, vomiting, diarrhoea, constipation, neutropenia, thrombocytopenia, anaemia, alopecia. Liver function test abnormalities, hyperbilirubinaemia. Laryngo-pharyngeal dysaesthesia (dysphagia, dyspnoea, jaw spasm), paraesthesia. Allergic reaction (rash, urticaria), anaphylaxis.
Fluorouracil
Diarrhoea, stomatitis, alopecia, palmer-plantar erythrodysesthesia (hand-foot syndrome). Chest pain, tachycardia.

Investigations

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Medical Assessment	X		X		X	Alternate cycles
Nursing Assessment	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	Repeat if clinically indicated
Dihydropyrimidine dehydrogenase (DPD) deficiency test	X					This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency.
CT/ PET CT scan	X					After completion of neo-adjuvant treatment (usually arranged by surgical team
Informed Consent	X					
Blood pressure*	X					Repeat if clinically indicated
PS recorded	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management

Haematological Toxicity

Proceed on day 1 if:-

ANC ≥ 1.5 x 10^9/L	Platelets ≥ 100 x 10^9/L

Delay 1 week on day 1 if:-

ANC ≤ 1.49 x 10^9/L	Platelets ≤ 99 x 10^9/L

If WCC, platelets or ANC still below required levels for treatment at week 2, delay treatment again and patient will need assessment and chemotherapy dose reduction as follows.

Lowest count since previous cycle	1st Incidence	2nd Incidence
Grade 3 / 4 neutropenia (<1.0 x10^9/L)	25% dose reduction	50% dose reduction

Non-haematological, non-neurologic toxicity

The dose of chemotherapy should be reduced to 75% for non-haematological toxicities exceeding grade 2 and to 50% if toxicities recurred after the first dose reduction.

Hepatic impairment

Docetaxel
If bilirubin > 22mmol/l or ALT/AST > 3.5 x ULN and ALP > 6 x ULN not recommended – delay treatment and refer to consultant
Oxaliplatin
Consider dose reduction if bilirubin > 26µmol/L. Not recommended in patients with bilirubin >51µmol/L. Renally excreted therefore no dose adjustments necessary.
Fluorouracil
Contra-indicated if bilirubin > 5x ULN.

Renal impairment

Docetaxel
No dose adjustment required for moderate renal impairment.
Oxaliplatin
Contra-indicated if CrCl < 30ml/min (no safety data). Consider dose reduction for patients with moderate renal impairment (< 60ml/min).
Fluorouracil
Consider dose reduction in severe renal impairment (< 30ml/min).

References:

Al-Batran SE 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).

Al-Batran SE et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol*. 2016; 12: 1697-1708

Al-Batran SE et al; Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Annals of Oncology 2008; 19: 1882-1887

Docetaxel 20 mg/ml concentrate for solution for infusion.

Summary of Product Characteristics. Seacross Pharmaceuticals Ltd, Bedford 23/03/2016.
Available from https://www.medicines.org.uk/emc last updated 24/05/2016

Fluorouracil 25 mg/ml injection.
Summary of Product Characteristics. Hospira UK Ltd, Warwickshire 19/07/2004.
Available from https://www.medicines.org.uk/emc last updated 24/09/14.

Oxaliplatin 5mg/ml Powder for Solution for Infusion.
Summary of Product Characteristics. Accord Healthcare Ltd Middlesex 11/09/2008.
Available from https://www.medicines.org.uk/emc last updated 08/02/2012.

Dosage Adjustment for Cytotoxics in Renal and Hepatic Impairment. University College London Hospital NHS Foundation Trust January 2009.

Cancer Chemotherapy: Guidelines for the administration of chemotherapy and the nursing care of cancer patients (6th Edition)