FLOT

Peri-operative use in resectable gastric or gastro-oesophageal junction adenocarcinoma
Suitable for fit patients only, with PS 0 - 1

Drugs/Dosage:	Docetaxel	50mg/m^2	IV	Day 1
	Oxaliplatin	85mg/m^2	IV	Day 1
	Calcium folinate (Folinic acid)	350mg	IV	Day 1
	Fluorouracil	2600mg/m^2	IV	continuous infusion over (24 hours) **over 46 hours until 24 hour pump available**

Administration:
Docetaxel in 250ml 0.9% sodium chloride over 1 hour
Flush with glucose 5%
Oxaliplatin in 250ml glucose 5% over 2 hours
concurrently with calcium folinate in 250ml glucose 5% over 2 hours
Flush with glucose 5%
5FU infusion via CVC and ambulatory infusion device over 24 hours (**46hr until 24hr pump available)**
Primary G-CSF prophylaxis s/c once daily for 5 days, starting on Day 4

Docetaxel pre-medication:
Dexamethasone 8mg po once daily in the morning for 4 days, commencing the morning of the day prior to docetaxel.
If the patient has not taken the oral pre-med for any reason, intravenous dexamethasone is not recommended and can only be substituted if prescribed by a Consultant.

Frequency:
2 weekly cycle
Perioperative use: 4 cycles before surgery, plus a further 4 cycles after surgery.

Main Toxicities:
myelosuppression; alopecia; diarrhoea; mucositis;
neurotoxicity (see Comments); palmar-plantar erythema (PPE);
coronary artery spasm (see Comments); allergic reaction to oxaliplatin;
docetaxel infusion-related reactions (↑ risk with 1st/2nd treatment); fluid retention;
myalgia/arthralgia; skin reactions & nail changes; ovarian failure/infertility

Anti-emetics:
highly emetogenic (anti-emetic dexamethasone pre and post chemotherapy not required due to docetaxel pre-med)

Extravasation:
non-vesicants

Regular Investigations:	FBC	Day 1
	LFTs & U&Es	Day 1
	Mg^{2+}	Day 1 (ideally, correct any low Mg^{2+} before oxaliplatin given)

Comments:
Oxaliplatin and Neurotoxicity
a) *Acute Cold-related Dysaesthesia (CRD):*
Many patients experience transient paraesthesia of hands & feet, and some experience 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 patient should be well advised on precautions to be taken. Does not require treatment or dose reduction.

Reason for Update: N/A	Approved by Consultant: Dr M Hewish
Version: 1	Approved by Lead Chemotherapy Nurse: S Wills-Percy
Supersedes: None	Date: 7.9.17
Prepared by: S Taylor	Checked by: C Tucker

For laryngopharyngeal dysaesthesia, subsequent infusions should be given over 6 hours. Consideration to infusion of 10mmol of magnesium + 1gram of calcium gluconate in 0.9% sodium chloride 250ml over 1 hour, prior to starting the oxaliplatin, should also be made. NB. The above management should **not** be used to try and alleviate CRD or cumulative neuropathy.

b) *Cumulative dose related peripheral sensory neuropathy:*
Usually occurs after a cumulative dose of 800mg/m^2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approx 3 – 5 months to recovery.

Coronary artery spasm is a recognised complication of 5FU although the evidence base regarding aetiology, management and prognosis is not particularly strong. Coronary artery spasm is more common in patients receiving continuous infusions of 5FU, and is usually reversible on discontinuing the infusion. Should a patient receiving 5FU present with chest pains, stop the 5FU. 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 5FU should be withdrawn permanently.[1] Refer to Consultant to discuss.

Dose Modifications

Haematological Toxicity:	Neutrophils < 1.5 x 10^9/l or Platelets < 100 x 10^9/l	Delay next cycle until recovered, then proceed, with dose reductions as applicable, as indicated below

Consider dose reduction of oxaliplatin and docetaxel to 75% dose (and to 50% dose if toxicity recurs after 1st dose reduction) in the event of febrile neutropenia despite adequate G-CSF support, or thrombocytopenia causing bleeding. Refer to Consultant to discuss.

Neurological Toxicity:
If neurological symptoms occur, use the following oxaliplatin dose adjustment guidelines:
Paraesthesia without functional impairment persisting until next cycle; reduce oxaliplatin dose by 25%
Paraesthesia with functional impairment or pain, reduce oxaliplatin dose by 50%
Paraesthesia with functional impairment or pain, and persisting until the next cycle, oxaliplatin should be discontinued.

Other Toxicities:
Grade 3+ diarrhoea or mucositis: reduce 5FU and docetaxel doses by 25% for remaining cycles.
If Grade 3/4 PPE occurs, consider a 20 – 25% dose reduction for 5FU in subsequent cycles. If in doubt, discuss with consultant.
In the event of other Grade 3+ non-haematological toxicities, dose reduce all 3 drugs to 75% dose (and to 50% dose if toxicity recurs after 1st dose reduction)

Myalgia / arthralgia due to docetaxel: often co-exist, usually Grade 1 or Grade 2. Management consists of reassuring patients that it is self-limiting. Consider use of NSAIDs, although not always effective.

Renal Impairment:
Oxaliplatin may be used at 100% dose in moderate renal impairment (CrCl > 30ml/min), but monitor renal function and dose adjust according to toxicity.
Omit oxaliplatin if CrCl < 30ml/min.

Hepatic Impairment:

Bilirubin > 22 μmol/l
or
ALT/AST > 3.5 x ULN
with
ALP > 6 x ULN

Docetaxel not recommended - may only be administered with consultant approval

Moderate hepatic impairment	Reduce initial 5FU dose by 1/3
Severe hepatic impairment	Reduce initial 5FU dose by ½

Increase dose if no toxicity. If in doubt, check with relevant consultant.

Probably no dose reduction necessary for oxaliplatin; clinical decision

Reference:

Al-Batran et al; Proceedings ASCO 2017; JCO 35 (supplement); abstract 4004
Al-Batran et al; Lancet Oncology 2016; 17: 1697 – 1708
Al-Batran et al; Annals of Oncology 2008; 19 (11): 1882 – 1887