Chemotherapy Protocol

UPPER GASTROINTESTINAL CANCER

DOCETAXEL-FLUOROURACIL-FOLINIC ACID-OXALIPLATIN

(FLOT)

Regimen

- Upper GI – Docetaxel-Fluorouracil-Folinic Acid-Oxaliplatin (FLOT)

Indication

- Perioperative treatment for patients with resectable oesophagogastric [gastric or gastroesophageal junction (GEJ)] adenocarcinoma
- WHO Performance status 0, 1

Toxicity

Drug	Adverse Effect
Docetaxel	Hypersensitivity, fluid retention, neuropathy, joint pains, nail changes, fatigue
Fluorouracil	Palmar-plantar erythrodysesthesia, diarrhoea, mucositis, chest pain
Oxaliplatin	Peripheral neuropathy (cumulative), acute laryngopharyngeal dysasthesia (increase duration of infusion)

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC, LFT's and U&E's prior to day one of treatment.
- Patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with fluorouracil. All patients should be tested for DPD deficiency before initiation (cycle 1) to minimise the risk of these reactions

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, where appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only. Deteriorating organ function may be a sign of disease progression.

Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L)

Prior to prescribing day one the following treatment criteria must be met;

Criteria	Eligible Level
Neutrophil	equal to or more than $1x10^9$/L (unless due to bone marrow impairment)
Platelets	equal to or more than $100x10^9$/L (unless due to bone marrow impairment)

If these levels are not achieved wait seven days and if recovered resume treatment with the following dose reductions

Dose Reductions

Drug	Starting Dose (mg/m^2)	Dose Level 1 (mg/m^2)	Dose Level 2 (mg/m^2)
Docetaxel	50	40	30
Fluorouracil	2600	2000	1600
Oxaliplatin	85	65	50

Neutrophil Count ($x10^9$/L)	Docetaxel	Fluorouracil	Oxaliplatin
0.5-0.99	Reduce by 1 dose level	Maintain Dose	Reduce by 1 dose level
Less than 0.5	Reduce by 1 dose level	Reduce by 1 dose level	Reduce by 1 dose level

Platelet Count ($x10^9$/L)	Docetaxel	Fluorouracil	Oxaliplatin
10-49.9	Reduce by 1 dose level	Maintain Dose	Reduce by 1 dose level
Less than 10	Reduce by 1 dose level	Maintain Dose	Reduce by 2 dose level

There is no need to dose adjust the folinic acid for haematological toxicity.

Hepatic Impairment

Drug	Bilirubin (µmol/L)		AST/ALT (units)		ALP (units)	Dose (% of original dose)
Docetaxel	N/A		Greater than1.5xULN	and	Greater than 2.5xULN	Give 75%
	Greater than ULN	and / or	Greatre than 3.5xULN	and	Greater than 6xULN	Not recommended

Drug	Bilirubin µmol/L	AST/ALT units	Dose
Fluorouracil	More than 85	More than 180	Contra-indicated
			In moderate hepatic impairment reduce the initial dose by 33%. In severe hepatic impairment reduce the initial dose by 50%. The dose may be increased as tolerated.

Drug	Dose
Oxaliplatin	Limited information available but there is probably little need to adjust the dose.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Docetaxel	N/A	No dose adjustment needed
Fluorouracil		Consider dose adjustment in severe renal impairment
Oxaliplatin		Moderate renal impairment – treat at normal dose, and monitor renal function. Dose adjust according to toxicity. CrCl <20m/min – dose reduce

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes. Dose limiting toxicities include diarrhoea, abdominal

pain, emesis, stomatitis, palmar-plantar erythrodysesthesia and neurosensory toxicities among others.

If any NCI-CTC grade 1toxicity occurs treatment should be continued, without interruption, at the full dose.

For toxicities at NCI-CTC grade 3 or above treatment should be withheld until recovery to NCI-CTC grade 1 then re-started if medically appropriate. If recovery takes 21 days or longer stop treatment.

Fluorouracil

Diarrhoea occurring for the first time at NCI-CTC grade 2 should be approached by withholding the fluorouracil until it has resolved to NCI-CTC grade 1. Treatment can then be re-started at full dose. Treatment should again be delayed on development of a second NCI-CTC grade 2 diarrhoea and the fluorouracil re-started at 75% of the original dose when it has resolved to NCI-CTC grade 1. After resolution of a third episode of NCI-CTC grade 2 diarrhoea to NCI-CTC grade 1 the fluorouracil should be re-started using 50% of the original dose.

On appearance of a NCI-CTC grade 3 diarrhoea withhold fluorouracil until it has resolved to NCI-CTC grade 1 and re-start treatment using 75% of the original dose. After a second episode at NCI-CTC grade 3 wait until the diarrhoea has resolved to NCI-CTC grade 1 and resume the fluorouracil using 50% of the original dose. For a third appearance of NCI-CTC grade 3 diarrhoea or the development of grade 4 toxicity at ant time stop fluorouracil therapy.

Oxaliplatin

If NCI-CTC grade 3-4 diarrhoea or stomatitis recurs despite appropriate reduction in the fluorouracil dose the oxaliplatin dose should be reduced to 75mg/m^2.

There are rare case reports of acute interstitial lung disease or lung fibrosis in association with oxaliplatin. Where an unexplained respiratory symptom occurs stop treatment until pulmonary investigations have been conducted to exclude an interstitial cause.

Docetaxel

Lacrimation

Excessive lacrimation is related to cumulative docetaxel doses and occurs after a median of 400mg/m^2. Symptomatic treatment with hypromellose 0.3% eye drops four times a day may help. However, if the ocular irritation continues consider reducing the docetaxel dose.

Skin

Delay the docetaxel where a NCI-CTC grade 3 cutaneous toxicity is present on day one of the cycle until it resolves to NCI-CTC grade 1 or below. The subsequent doses of docetaxel should be reduced. If it occurs with a reduced dose or if there is no recovery after two weeks, docetaxel treatment should be stopped. Where a NCI-CTC grade 3 cutaneous toxicity occurs between cycles with recovery by day one

then reduce the docetaxel dose as described. Docetaxel should be stopped in response to a NCI-CTC grade 4 cutaneous toxicity.

Stomatitis

A NCI-CTC grade 2 stomatitis should result in a delay in treatment until it has become NCI-CTC grade 1 or below. Treatment may then be re-started at the previous dose. For a NCI-CTC grade 3 stomatitis delay treatment until it has recovered to NCI-CTC grade 1 or below then reduce the dose. Treatment should be stopped in relation to a NCI-CTC grade 4 stomatitis.

Hypersensitivity

Docetaxel hypersensitivity reactions tend to occur with the first or second infusion. For minor symptoms such as flushing or localised rashes the infusion should not be interrupted. For severe reactions including profound hypotension, bronchospasm and generalised erythema discontinue the infusion immediately

Peripheral Neuropathy

Neurosensory toxicity can occur with both docetaxel and oxaliplatin. The following table describes dose reductions for both agents. This tables applies where the neuropathy is NCI-CTC grade 3 or above or grade 2 that persist for longer than 7 days

Toxicity	Duration of toxicity 1-7 days	Duration of toxicity more than 7 days	Persistent between cycles
Cold-related dysesthesia	No reduction	No reduction	Withhold until recovery then restart at 75% dose for oxaliplatin and docetaxel.
Paraesthesia without pain	No reduction	No reduction	Withhold until recovery then restart at 75% dose for oxaliplatin and docetaxel
Paraesthesia with pain or functional impairment	No reduction	Reduce to 75% dose on subsequent cycles and discuss with consultant Omit oxaliplatin and docetaxel if recurs	Omit oxaliplatin and docetaxel and discuss with consultant

Regimen

14 day cycle for 4 cycles then surgery should occur. A further 4 cycles should be prescribed post operatively. 8 cycles will be set in ARIA.

Drug	Dose	Days	Administration
Docetaxel	50mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
Fluorouracil	2600mg/m^2	1	Intravenous infusion over 24 hours
Folinic Acid	350mg	1	Intravenous infusion in 250ml glucose 5% over 120 minutes
Oxaliplatin	85mg/m^2	1	Intravenous infusion in 500ml glucose 5% over 120 minutes

Dose Information

- Docetaxel will be dose banded as per the national dose bands (20mg/ml)

  Docetaxel induced fluid retention can lead to weight gain. This is not a reason to alter the dose.

- Fluorouracil will be dose banded as per the national dose bands (50mg/ml)

- Oxaliplatin will be dose banded as per the national dose bands (5mg/ml)

Administration Information

Extravasation

- Fluorouracil – inflammitant
- Oxaliplatin – exfoliant
- Docetaxel – exfoliant

Other

- Central venous access and use of an ambulatory infusion pump is required.

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy

  - ondansetron 8mg oral or intravenous

As take home medication;

- metoclopramide 10mg three times a day when required oral

- ondansetron 8mg twice a day oral starting on the evening of the day of chemotherapy

- Oral loperamide 4mg after the first loose stool then 2-4mg four times a day when required for the relief of diarrhoea (maximum 16mg/24 hours).

- Gastric protection with a proton pump inhibitor or H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

- To prevent fluid retention and hypersensitivity reactions prescribe dexamethasone 8mg twice a day oral for three days starting 24 hours before docetaxel administration. On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg

Additional Information

- A glucose 5% flush should be administered before and after the oxaliplatin

- The folinic acid may be replaced with calcium levofolinate 175mg intravenous infusion in 250ml glucose 5% over 120 minutes

References
1. Al-Batran SE, Homann N, 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). ASCO 2017; 35: 4004.

REGIMEN SUMMARY

Docetaxel-Fluorouracil-Folinic Acid-Oxaliplatin (FLOT)

Cycles 1, 2, 3, 4, 5, 6, 7

Day Minus One 1

1. Dexamethasone 8mg twice a day oral*

Day One

2. Dexamethasone 8mg oral (from TTO)*
   Administration Instructions
   Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat, (10mg IV stat if on aprepitant)*, or equivalent dose, 15-30 minutes before chemotherapy.

3. Ondansetron 8mg oral or intravenous

4.Docetaxel 50mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
Administration Instructions
Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat, (10mg IV stat if on aprepitant)*, or equivalent dose, 15-30 minutes before chemotherapy.

5. Oxaliplatin 85mg/m^2 intravenous infusion in 500ml glucose 5% over 120 minutes

6. Folinic acid 350mg intravenous infusion in 250ml glucose 5% over 120 minutes

7. Fluorouracil 2600mg/m^2 intravenous infusion over 24 hours

Take Home Medicines

8. Dexamethasone 8mg twice a day oral for 3 days starting the day before the docetaxel infusion*

9. Metoclopramide 10mg three times a day when required oral
   Administration Instructions
   Please supply 28x10mg tablets or nearest equivalent pack size

10. Ondansetron 8mg twice a day for three days starting on the evening of the day of chemotherapy
   Administration Instructions
   Take 8mg twice a day for three days starting on the evening of day 1 of the cycle

Cycle 8

Day Minus One 1

11. Dexamethasone 8mg twice a day oral*

Day One

12. Dexamethasone 8mg oral (from TTO)*

Administration Instructions
Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat, (10mg IV stat if on aprepitant)*, or equivalent dose, 15-30 minutes before chemotherapy.

13. Ondansetron 8mg oral or intravenous

14.Docetaxel 50mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes

Administration Instructions
Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat, (10mg IV stat if on aprepitant)*, or equivalent dose, 15-30 minutes before chemotherapy.

15. Oxaliplatin 85mg/m^2 intravenous infusion in 500ml glucose 5% over 120 minutes

16. Folinic acid 350mg intravenous infusion in 250ml glucose 5% over 120 minutes

17. Fluorouracil 2600mg/m^2 intravenous infusion over 24 hours

Take Home Medicines

18. Metoclopramide 10mg three times a day when required oral

Administration Instructions
Please supply 28x10mg tablets or nearest equivalent pack size

19. Ondansetron 8mg twice a day for three days starting on the evening of the day of chemotherapy

Administration Instructions
Take 8mg twice a day for three days starting on the evening of day 1 of the cycle

In Aria Planner the dexamethasone 8mg twice daily will appear on days 1, 2, 3 of treatment. This is the supply for the next cycle. The patient should have been given the supply for cycle one in the pre-assessment or consent clinic. The administration instructions reflect this.

DOCUMENT CONTROL

Version	Date	Amendment	Written/ By	Approved By
1.1	Nov 2020	Updated monitoring with DPD testing Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1	August 2018	None	Stuart Martin Pharmacist Dr Deborah Wright Pharmacist	Dr Tim Iveson Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.