Chemotherapy Protocol

NSCLC CANCER

DOCETAXEL-NINTEDANIB

Regimen

- NSCLC – Docetaxel-Nintedanib

Indication

- Advanced or metastatic NSCLC of adenocarcinoma origin that has progressed after platinum-based combination regimen
- WHO Performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Docetaxel	Hypersensitivity, fluid retention, neuropathy, joint pains, nail changes, fatigue
Nintedanib	Haemorrhage, venous thromboembolism

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

Monitoring

Regimen

- FBC, U&E's and LFT's prior to each cycle

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 if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

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

Criteria	Eligible Level
Neutrophil	equal to or more than $1.5x10^9$/L (unless due to bone marrow involvement)
Platelets	equal to or more than $100x10^9$/L (unless due to bone marrow involvement)

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

The dose of nintedanib does not need to be reduced for haematological toxicity.

Toxicity	Grade (NCI-CTC)	Docetaxel ($75mg/m^2$)	Docetaxel ($60mg/m^2$)
Neutrophil	1	$75mg/m^2$	$60mg/m^2$
	2	Delay until grade 1 then $75mg/m^2$	Delay until grade 1 then $60mg/m^2$
	3	Delay until grade 1 then $75mg/m^2$	Delay until grade 1 then $60mg/m^2$
	4	Delay until grade 1 then $60mg/m^2$	Stop
Febrile Neutropenia	3	Delay until grade 1 then $60mg/m^2$	Stop
	4	Delay until grade 1 then $60mg/m^2$	Stop
Platelets	Greater than or equal to $100x10^9$/L	$75mg/m^2$	$60mg/m^2$
	Less than $100x10^9$/L	Delay until greater than or equal to $100x10^9$/L then $60mg/m^2$	Stop

Kidney Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Docetaxel	N/A	No dose adjustment needed
Nintedanib	N/A	Safety in those with a CrCl of less than 30ml/min is not established

Liver Impairment

Drug	Bilirubin (µmol/L)		AST/ALT (units)		Alk Phos (units)	Dose (% of original dose)
Docetaxel	N/A		1.5xULN or greater	and	2.5xULN or greater	Give 75%
	Greater than ULN	and/or	3.5xULN or greater	and	6xULN or greater	Not Recommended

Nintedanib	There is no safety data in those with Child Pugh B or C hepatic impairment

Should liver impairment occur during treatment then dose adjust as below.

AST / ALT and bilirubin elevations	Dose adjustment
Elevation of AST and/or ALT values to more than 2.5xULN in conjunction with total bilirubin elevation equal to or greater than 1.5xULN or elevation of AST and/or ALT values to more than 5xULN	After treatment interruption and recovery of transaminase-values to less than or equal to 2.5xULN in conjunction with bilirubin to normal, dose reduction from 200 mg twice daily to 150 mg twice daily and, if a 2nd dose reduction is considered necessary from 150 mg twice daily to 100 mg twice daily.
Elevation of AST and/or ALT values to more than 3xULN in conjunction with an increase of total bilirubin to more than 2x ULN and ALKP less than 2xULN	Unless there is an alternative cause established, nintedanib should be permanently discontinued

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.

Docetaxel

Peripheral neuropathy at NCI-CTC grade 3 should result in a dose reduction from 75mg/m^2 to 60mg/m^2 once the neuropathy has resolved to NCI-CTC grade 2 or below. If the NCI-CTC grade 3 neuropathy occurred at doses lower than 75mg/m^2 or a NCI-CTC grade 4 toxicity develops consider stopping treatment.

Excessive tearing / lacrimation are related to cumulative docetaxel doses and occur 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 reduce the docetaxel dose to 80% of the original dose in the first instance.

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 from 75mg/m^2 to 60mg/m^2. If it occurs with a dose of 60mg/m^2 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.

Nintedanib

CTCAE* Adverse Reaction	Dose Adjustment
Diarrhoea equal to or greater than CTC grade 2 for more than 7 consecutive days despite anti-diarrhoeal treatment ***Or*** diarrhoea equal to or greater than grade 3 despite anti-diarrhoeal treatment	After treatment interruption and recovery to grade 1 or baseline, dose reduction from 200 mg twice daily to 150 mg twice daily and, if a 2nd dose reduction is considered

Vomiting equal to or greater than grade 2 ***and / or*** nausea greater than or equal to grade 3 despite anti-emetic treatment	necessary, from 150 mg twice daily to 100 mg twice daily.
Other non-haematological or haematological adverse reaction of greater than or equal to grade 3	

Regimen

Docetaxel is highly myelosuppressive and in those with poor bone marrow reserves (for example due to extensive prior treatment, bone metastasis or extensive skeletal radiation) consider a starting dose of 55mg/m² with a view to increase to 75mg/m² if well tolerated.

21 day cycle for 4 cycles (docetaxel). Nintedanib can be continued until intolerance or disease progression occurs (an additional 8 cycles will be set in Aria, making twelve cycles in total)

Drug	Dose	Days	Administration
Docetaxel	75mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
Nintedanib	200mg twice a day	Continuous	Oral

Dose Information

- Docetaxel will be dose banded as per the CSCCN agreed bands
- Docetaxel induced fluid retention can lead to weight gain. This is not a reason to alter the doses

Administration Information

Hypersensitivity reactions tend to occur with the first or second infusion of docetaxel. The docetaxel infusion should not be interrupted for minor symptoms such as flushing or localised rashes. Immediately discontinue the infusion for severe reactions which include profound hypotension, bronchospasm and generalised erythema.

- Docetaxel doses of more than 200mg should be diluted in 500ml sodium chloride 0.9% (maximum concentration 0.74mg/ml)
- Nintedanib should not be administered on the same day as docetaxel.

Extravasation

- Docetaxel – exfoliant

Additional Therapy

- Antiemetics

  15-30 minutes before docetaxel

  - metoclopramide 10mg oral or intravenous

  As take home medication

  - metoclopramide 10mg three times a day when required oral

- To prevent fluid retention and hypersensitivity reactions prescribe dexamethasone 8mg twice a day orally for three days starting 24 hours before the docetaxel administration. On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg, or nearest equivalent dose, once only intravenous bolus.

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

Coding

- Procurement – X70.8
- Delivery – X72.9

References

1. Reck M, Kaiser R, Mellemgaard A et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small cell lung cancer (LUME – lung 1): a phase three, double blind randomised controlled trial. Lancet Oncol 2014; 15 (2): 143-155.

REGIMEN SUMMARY

Docetaxel-Nintedanib

Cycle 1, 2, 3

Day Minus One

1. Dexamethasone 8mg twice a day oral*

Day One

2. Dexamethasone 8mg twice a day oral (from TTO)*

3. Metoclopramide 10mg oral or intravenous

4. Docetaxel 75mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes

Take Home Medicines

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

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

7. Nintedanib 200mg twice a day oral starting on day two of the cycle
   Administration Instructions
   Do not take nintedanib on the day of docetaxel administration.

Cycle 4

Day Minus One

8. Dexamethasone 8mg twice a day oral*

Day One

9. Dexamethasone 8mg twice a day oral (from TTO)*

10. Metoclopramide 10mg oral or intravenous

11. Docetaxel 75mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes

Take Home Medicines

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

13. Nintedanib 200mg twice a day oral starting on day two of the cycle
    Administration Instructions
    Do not take nintedanib on the day of docetaxel administration

Cycle 5 – 12 inclusive

Take Home Medicines

14. Nintedanib 200mg twice a day oral

* 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 administration instructions reflect this. On the last cycle no dexamethasone will appear for prescribing.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Oct 2015	None	Dr Debbie Wright Pharmacist	Dr Andrew Bates Consultant Clinical 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 Hospital 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 which occur as a result of following these guidelines.