

Lung Pathway Group – Cisplatin & PO Vinorelbine in Non-Small Cell Lung Cancer (NSCLC)

Indication: First line in radical/induction treatment in locally advanced NSCLC
First line palliative treatment in advanced/metastatic NSCLC
Eligible for patients able to tolerate and comply with oral dosage forms

Regimen details:

Cisplatin	75 - 80 mg/m ² IV	Day 1
Vinorelbine	60mg/m ² PO	Day 1 & Day 8 (first cycle)
*Vinorelbine	80mg/m ² PO	Day 1 & Day 8 (second cycle onwards)

* See dose escalation guidance under 'Dose modifications' -
*Note: Vinorelbine dose escalation is **not** indicated in advanced disease or palliative treatment intent, unless vinorelbine is used as monotherapy.*
*Dose escalation to 80mg/m² does **not** take place with concomitant radiotherapy; when combined with radiotherapy, vinorelbine dose is reduced to 50-75% dose, depending on clinical oncologist's recommendations. 2 or 3 cycles of radiotherapy may be given concomitantly with chemotherapy.*

Administration: Suggested hydration schedule:

Day 1

Furosemide 40mg orally
1 litre 0.9% Sodium Chloride + 20 mmol KCl + 1g MgSO₄ IV over 60 minutes
Cisplatin in 1 litre Sodium Chloride 0.9% IV over 2 hours
1 litre Sodium Chloride 0.9% + 40 mmol KCl + 1g MgSO₄ IV over 2 hours
Then **either** 500ml Sodium Chloride 0.9% IV over 60 minutes **or** 500ml drinking water

Version: 1.0 Supersedes: all other versions	Approved by LCA Lung Pathway Chemotherapy Lead: Dr Rohit Lal	
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl	
Prepared by: Lisa Yuen	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson	
Second check by: Laura Cameron	Date prepared: November 2014	Review Date: November 2016
<p>Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.</p> <p>©LCA Copyright 2014</p>		

Encourage oral hydration during treatment; for instance drink a glass of water every hour during treatment, and **at least a further 2 litres over the 24 hours following treatment.**

Weight should be recorded prior to and at the end of cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and cisplatin infusion should not be commenced unless this urine output is achieved. For low urine output consider increasing the pre-hydration and diuretic regimen. Consider adding diuretics in weight-gain of 1.5 kg, or symptoms of fluid overload.

Aluminium containing equipment should not be used during preparation and administration of cisplatin.

Hypersensitivity reactions may occur, such as flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and fever or chills, usually during the first and second infusions and within a few minutes following the start of the infusion; the infusion should be slowed down or interrupted and the necessary supportive medication should be administered.

Severe reactions such as hypotension and/or bronchospasm or generalised rash/erythema requires immediate discontinuation. Availability of resuscitation equipment must be ensured as a standard precaution.

Vinorelbine available as 20mg, 30mg and 80mg soft capsules. Capsules to be swallowed whole with water without chewing or sucking. Capsules are recommended to be taken with food.

Frequency:	Day 1 and Day 8, every 21 days
Induction/adjuvant	Total of 4 cycles; 2 to 3 cycles may be given concomitantly with radiotherapy
Advanced/palliative	Total of 4 to 6 cycles
Pre-medication:	Not routinely required
Anti- emetics:	Day 1: High emetogenicity Day 8: Low emetogenicity

Version: 1.0 Supersedes: all other versions	Approved by LCA Lung Pathway Chemotherapy Lead: Dr Rohit Lal	
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl	
Prepared by: Lisa Yuen	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson	
Second check by: Laura Cameron	Date prepared: November 2014	Review Date: November 2016
<p>Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.</p> <p>©LCA Copyright 2014</p>		

Follow local anti-emetic policy

Supportive medication: Mouthcare as per local policy
Paracetamol / Chlorphenamine / Hydrocortisone can be given for administration-related reactions such as chills / fever.

Extravasation: Cisplatin is non-vesicant

Regular investigations: Prior to Cycle 1:

FBC	Day 1 (within 14 days)
LFTs	Day 1 (within 14 days)
U&Es	Day 1 (within 14 days)
Ca & Mg	Day 1 (within 14 days)
CT scan	Baseline
EDTA	See comments
Audiogram	If clinically indicated

Comments:

GFR should be calculated using the Cockcroft & Gault formula; if the calculated GFR <60 or >120ml/min measure EDTA clearance before prescribing. Monitor trends in serum creatinine between treatments, if >25% from baseline value re-calculate GFR using the Cockcroft & Gault formula.

Prior to Day 8 (all cycles):
FBC Day 8 (within 48 hours)

Prior to Day 1 (all cycles):
FBC Day 1 (within 72 hours)
LFTs Day 1 (within 72 hours)
U&Es Day 1 (within 72 hours)
Imaging* After 3 cycles

*Imaging not required in the adjuvant setting

Toxicities: Myelosuppression, ovarian failure/infertility, peripheral neuropathy and neuropathy induced constipation, alopecia (usually mild), GI symptoms, nausea and vomiting, myalgia, fatigue, neurotoxicity (ototoxicity), nephrotoxicity, encephalopathy, electrolyte imbalances.

Version: 1.0 Supersedes: all other versions	Approved by LCA Lung Pathway Chemotherapy Lead: Dr Rohit Lal
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Lisa Yuen	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Laura Cameron	Date prepared: November 2014 Review Date: November 2016
<p>Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.</p> <p>©LCA Copyright 2014</p>	

DOSE MODIFICATIONS**Haematological Toxicity****Prior to day 1**

Neutrophils (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Cisplatin Dose	Vinorelbine Dose
≥ 1.5	&	≥ 100	100% dose	100% dose
< 1.5	&/or	< 100	Delay for 1 week. Repeat FBC, if recovered to above these levels give 100% dose.	Delay for 1 week. Repeat FBC, if recovered above these levels give 100% dose.

If neutrophils < 0.5 x 10⁹/L for more than 5 days or < 0.1 x 10⁹/L for more than 3 days,
or platelets < 25 x 10⁹/L,
or febrile neutropenia is diagnosed,
or toxicity related delay is > 1 week
- vinorelbine dose should be reduced to 75% from previous dose (do not escalate for subsequent cycles).

Prior day 8

Neutrophils (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Vinorelbine Dose
≥ 1.0	&	≥ 100	Give 100% dose
< 1.0	or	< 100	Omit

Vinorelbine Dose escalation after 1st cycle in Adjuvant/ Induction setting (not for RT patients)

If the first cycle is well tolerated, it is recommended to increase the dose of vinorelbine to 80mg/m² at cycle 2 in the following settings:

Adjuvant/ induction setting, and when vinorelbine is used as a single agent.

When relevant, dose escalation should take place at cycle 2 only if:

- no grade 4 neutropenia (<0.5 x 10⁹/L) at day 8.
- no febrile neutropenia

Dose escalation should **NOT** occur in the palliative treatment of advanced disease unless vinorelbine is used as monotherapy, or for patients who are having concomitant chemotherapy regimen.

Vinorelbine Dose de - escalation from 2nd cycle onwards in Adjuvant/ Induction setting

If grade 4 neutropenia (<0.5 x 10⁹/L) occurs during cycles with 80mg/m² dose, delay treatment until recovered, then reduce to 60mg/m².

It is possible to re-escalate the dose after further 3 administrations with lower dose if well tolerated. Follow monitoring in following cycles as detailed above.

Version: 1.0 Supersedes: all other versions	Approved by LCA Lung Pathway Chemotherapy Lead: Dr Rohit Lal	
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl	
Prepared by: Lisa Yuen	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson	
Second check by: Laura Cameron	Date prepared: November 2014	Review Date: November 2016
<p>Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.</p> <p>©LCA Copyright 2014</p>		

Non-haematological Toxicities**Renal Impairment**

Creatinine Clearance (ml/min)	Cisplatin Dose
≥ 60	Give 100% dose
< 60	Contraindicated – consider carboplatin

Vinorelbine: Dosage adjustment not required

Hepatic Impairment

Cisplatin: No dose modifications required

Vinorelbine:

If hepatic insufficiency is due to metastatic involvement, liver function may recover in response to treatment. Therefore, for patients with massive liver metastases, i.e. >75% of liver volume replaced by tumour, it is empirically suggested that the dose of vinorelbine be reduced to 85% dose and haematological toxicity closely followed up.

If hepatic insufficiency is due to other reasons, the table below should be used:

Bilirubin	ALT / AST	Vinorelbine Dose
< 1.5 x ULN	< 5 x ULN	Give 100% dose
1.5 – 3 x ULN	5 – 20 x ULN	Delay day 1 for 1 week/omit day 8, and reassess*. Consider dose reduction to 25-50% dose.
> 3 x ULN	> 20 x ULN	Discontinue

*If liver toxicity persists for more than 3 weeks, discontinue treatment

Dose modifications for other toxicities as appropriate**Neurotoxicity**

Neurotoxicity	Cisplatin Dose	Vinorelbine Dose
Grade 2	Give 50% dose	Give 100% dose
Grade 3 or 4	Discontinue	Discontinue

Other toxicities

	Cisplatin Dose	Vinorelbine Dose
Grade 3 mucositis	Give 100% of previous dose	Give 75% of previous dose
Grade 4 mucositis	Give 75% of previous dose	Give 50% of previous dose

Version: 1.0 Supersedes: all other versions	Approved by LCA Lung Pathway Chemotherapy Lead: Dr Rohit Lal	
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl	
Prepared by: Lisa Yuen	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson	
Second check by: Laura Cameron	Date prepared: November 2014	Review Date: November 2016

Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.

Any grade 3 toxicities (except mucositis), or diarrhoea (any grade) requiring hospitalisation	Give 75% of previous dose	Give 75% of previous dose
Any grade 4 toxicities (except mucositis)	Give 50% of previous dose	Give 50% of previous dose, or omit if Day 8 dose
Grade 3 oesophagitis with radiotherapy	Delay for 1 week, continue radiotherapy if possible	
Grade 3 or 4 constipation		Omit – consider substituting with gemcitabine

If patient suffers any Grade 3 or 4 toxicity after 2 dose reductions, treatment must be reviewed by consultant

Location of regimen delivery: Day case setting

Comments: Electrolyte disturbances – Cisplatin
Disturbances in electrolytes can be a long term manifestation due to the cisplatin induced renal tubular dysfunction. Check electrolytes - additional supplementation of magnesium, calcium or potassium may be required
Women of childbearing potential must use effective contraception during treatment.
Sexually mature males are advised not to father a child during the treatment, and up to 6 months thereafter. If appropriate, male patients should be advised to seek counselling on sperm storage before starting treatment.

Drug interactions: Itraconazole- increased risk of neurotoxicity
Posaconazole, voriconazole- increased vinorelbine plasma levels
Omeprazole and fluoxetine may inhibit vinorelbine metabolism
Phenytoin, carbamazepine – cisplatin decreases efficiency
Nephrotoxic drugs (with cisplatin)
Aminoglycoside antibiotics-increased risk of ototoxicity (with cisplatin)

References: www.medicines.org.uk
Krzakowski M *et al.* Oral vinorelbine and cisplatin as induction chemotherapy and concomitant chemo-radiotherapy in stage III non-small cell lung cancer : final results of an international phase III trial. J Thorac Oncol 2008 3(9) 994-1002

Version: 1.0 Supersedes: all other versions	Approved by LCA Lung Pathway Chemotherapy Lead: Dr Rohit Lal	
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl	
Prepared by: Lisa Yuen	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson	
Second check by: Laura Cameron	Date prepared: November 2014	Review Date: November 2016
<p>Disclaimer: The Joint Delivery Chemotherapy Nurse/Oncology Pharmacist Group is a sub-group of the Medicines & Chemotherapy Steering Group (MCSG) working within the London Cancer Alliance Integrated Cancer System (LCA). The output of the LCA MCSG includes documentation that can be adopted by healthcare organisations at their discretion. It is the responsibility of each individual organisation to ensure that appropriate governance and safety clearance procedures within their own clinical service have been followed prior to implementation of any such pieces of work. LCA assume no responsibility for this process within individual organisations, and no responsibility for the clinical management of individual patients or patient groups. Any clinical queries regarding individual patients or documentation should be directed to the relevant clinical team within the most appropriate healthcare organisation.</p> <p>©LCA Copyright 2014</p>		