Systemic Anti-Cancer Treatment Protocol

Cisplatin & Vinorelbine
Chemo-radiation Regimen
NSCLC

PROTOCOL REF: MPHACVCRLU
(Version No: 1.0)

Approved for use in:

Locally advanced (inoperable stage III) NSCLC

Dosage:

Dosage	Dose	Route	Frequency
Cisplatin	20mg/m^2	IV Infusion	Days 1 to 4 and 22 to 25
Vinorelbine	15mg/m^2		Days 1, 8, 19, 26
Followed at 4 to 6 weeks by:			
Cisplatin	80mg/m^2	IV Infusion	Day 1 every 21 days max. 2 cycles
Vinorelbine	25mg/m2 **(Maximum Dose: 50mg)**		Days 1 & 8 every 21 days max. 2 cycles

Supportive treatments for concurrent cis/vin

Dexamethasone 4mg oral tablets twice daily for 3 days following day 4 and day 25

Domperidone 10mg oral tablets three times a day as required

Supportive treatments for sequential cis/vin

Aprepitant 125mg oral on day 1 then 80mg oral tablets once daily for two days

Dexamethasone 4mg oral tablets twice daily for 3 days

Ondansetron 8mg oral tablets twice daily for 3 days

Domperidone 10mg oral tablets three times a day as required

Extravasation risk:

Cisplatin- irritant

Vinorelbine- vesicant

Refer to the CCC policy for 'Prevention and Management of Extravasation Injuries'.

Administration:

Check renal function before commencing cisplatin using Cockcroft and Gault Creatinine Clearance (CrCl) equation:

Calculate creatinine clearance using Cockcroft and Gault equation:

Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

CrCl must be ≥45 mL/min for cisplatin based treatment. Please ensure the dose has been adjusted if renal function is between 45 and 60 ml/min.

Interactions:

Aminoglycosides e.g. gentamicin, vancomycin and diuretics

Increased risk of nephrotoxicity and ototoxicity. Renal function should be well monitored and audiometric tests carried out as indicated.

Aprepitant

Aprepitant is theoretically predicted to increase the exposure of vinorelbine. Caution is advised. Consider alternative antiemetic if vinorelbine toxicity occurs.

Carbamazepine

Is predicted to decrease the exposure to vinorelbine. Manufacturer advises use with caution or avoid

Phenytoin

Vinorelbine, cisplatin and phenytoin increase the risk of peripheral neuropathy.

Phenytoin is predicted to decrease the exposure to vinorelbine.

Please consult summary of product characteristics via https://www.medicines.org.uk/emc for full list of interactions.

Concurrent chemotherapy and radiotherapy administration for 1 cycle ONLY:

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	8mg	oral	30 mins before chemotherapy
	Ondansetron	16mg	oral	30 mins before chemotherapy
	Vinorelbine	15mg/m^2	IV	In 50mL sodium chloride 0.9% over 10 minutes
	Sodium Chloride 0.9%	500mL	IV	Over 60 minutes
	Cisplatin	20mg/m^2	IV Infusion	In 1000mL sodium chloride 0.9% over 60 minutes
	Sodium Chloride 0.9%	500mL	IV	Over 60 minutes
2, 3 and 4	**Dexamethasone**	8mg	oral	30 mins before chemotherapy
	Ondansetron	16mg	oral	30 mins before chemotherapy
	Sodium Chloride 0.9%	500mL	IV	Over 60 minutes
	Cisplatin	20mg/m^2	IV Infusion	In 1000mL sodium chloride 0.9% over 60 minutes
	Sodium Chloride 0.9%	500mL	IV	Over 60 minutes
8 and 19	**Vinorelbine**	15mg/m^2	IV	In 50mL sodium chloride 0.9% over 10 minutes
8 and 19	Sodium Chloride 0.9%	250ml	IV as flush	
22, 23, 24 and 25	**Dexamethasone**	8mg	oral	30 mins before chemotherapy
	Ondansetron	16mg	oral	30 mins before chemotherapy
	Sodium Chloride 0.9%	500mL	IV	Over 60 minutes
	Cisplatin	20mg/m^2	IV Infusion	In 1000mL sodium chloride 0.9% over 60 minutes

	Sodium Chloride 0.9%	500mL	IV	Over 60 minutes
26	**Vinorelbine**	15mg/m^2	IV	In 50mL sodium chloride 0.9% over 10 minutes
26	Sodium Chloride 0.9%	250ml	IV as flush	

Ideally treatment should commence on a Monday see table below for corresponding day of treatment and fraction of radiotherapy

Treatment Day	Radiotherapy Fraction	Week day	Chemotherapy	Chemotherapy
1	1	MO	Cisplatin	Vinorelbine
2	2	TU	Cisplatin	
3	3	WE	Cisplatin	
4	4	TH	Cisplatin	
5	5	FR		
6		SA		
7		SU		
8	6	MO		Vinorelbine
9	7	TU		
10	8	WE		
11	9	TH		
12	10	FR		
13		SA		
14		SU		
15	11	MO		
16	12	TU		
17	13	WE		
18	14	TH		
19	15	FR		Vinorelbine
20		SA		
21		SU		
22	16	MO	Cisplatin	
23	17	TU	Cisplatin	
24	18	WE	Cisplatin	
25	19	TH	Cisplatin	
26	20	FR		Vinorelbine

If start date is delayed until Tuesday then day 6 onwards should commence the subsequent Monday.

If chemotherapy and radiotherapy are to be given on the same day please ensure chemotherapy is given before radiotherapy.

Followed at 4 – 6 weeks by:

Day	Drug	Dose	Route and rate
1	Aprepitant	125mg	PO 1 hour prior to commencing cisplatin
1	Dexamethasone	12mg	PO
1	Ondansetron	24mg	PO
1 Pre-hydration	Sodium Chloride 0.9%	**500mL**	IV over 1.5 hour
1	Monitor urine Output > 200mls/hr proceed		
1	Cisplatin in **1000mL** Sodium Chloride 0.9%	80mg/m^2	IV over **90 minutes**
1 Post-hydration	Sodium Chloride 0.9% **500mL**		IV over 90 minutes
1	Vinorelbine	25mg/m^2 **(Maximum Dose: 50mg)**	In 50mL sodium chloride 0.9% over 10 minutes
1	Sodium Chloride 0.9% **250ml**		IV as flush

Day	Drug	Dose	Route and rate
8	Vinorelbine	25mg/m^2 **(Maximum Dose: 50mg)**	In 50mL sodium chloride 0.9% over 10 minutes
8	Sodium Chloride 0.9%	250ml	IV as flush

Give 2 cycles at 21 day intervals

As with all platinum based chemotherapy, patients may experience allergic reaction during administration. Please refer to the CCC Hypersensitivity; Management Prevention Policy.

For severe reactions, discuss with Consultant before continuing with treatment.

It should be strongly noted that patients who have severe reactions should not be re-challenged.

Main Toxicities:

Highly emetogenic, myelosuppression, mucositis, diarrhoea, neurotoxicity, allergic reactions, cardiotoxicity, ovarian failure/infertility

Investigations and treatment plan

	Pre	Cycle 1			Cycle 2+3		Comments
		Day 1 and 19	Day 8	Days 2-4 and 22-26	Day 1	Day 8	
Clinical Assessment	X						Prior to cycle 1, at the end of radiotherapy and at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	Every administration
FBC	X	X	X		X	X	
U&E & LFT	X	X			X		
Serum magnesium and calcium	X	X			X		
CrCl (Cockcroft and Gault)	X	X			X		May be more frequently if clinically indicated e.g. vomiting
Informed Consent	X						
Weight recorded	X	X	X	X	X	X	Every administration
Height recorded	X						

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 and 19 if:

Platelets ≥ 100 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Proceed on day 8 if:

Platelets ≥ 75 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Non-haematological

Hepatic Impairment:

Vinorelbine	
Mild: bilirubin >1.0-1.5 x ULN and any AST or bilirubin ≤ULN and AST >ULN Moderate: bilirubin 1.5-3 x ULN, with any AST	No dose adjustment is needed
Severe bilirubin >3.0-10 x ULN, with any AST	Consider 66% of original dose

Cisplatin
No dose adjustment necessary

Renal Impairment:

Vinorelbine
No dose adjustment necessary

Calculate renal function using Cockcroft and Gault. If borderline, an EDTA should be requested.

Cisplatin	
CrCl (mL/min)	**Dose**
≥ 60 mL/min	Give 100%
45 to 59 ml/min	Give 75%
< 45 mL/min	Contraindicated

Inadequate urine output (< 200mls/hr):

- Administering 500ml Sodium Chloride +/- furosemide 20 - 40mg - furosemide 20 – 40mg orally may also be given if there is a positive fluid balance of 1.5 litres, a weight gain of 1.5kg or symptoms of fluid overload.
- The patient should be asked to drink 2 litres of fluid in the 24hrs following treatment, and to contact the hospital if this is impossible because of problems e.g. nausea and vomiting.

Neurotoxicity:

If patient develops Grade 2 neuropathy or ototoxicity, discuss with consultant. Cisplatin and vinorelbine can both cause neuropathy.

Patients with functional hearing loss should have cisplatin omitted, carboplatin AUC 3-5 can be substituted.

Cumulative:-Dose related peripheral sensory neuropathy: Usually occurs after a cumulative dose. It can occur after treatment with cisplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

References:

- https://www.medicines.org.uk/emc/product/311/smpc
- https://www.medicines.org.uk/emc/product/6111/smpc
- The Lancet: Dose recommendations for anticancer drugs with renal or hepatic impairment 2019
- J. Maguire, I. Khan, R. McMenemin, N. O'Rourke, S. McNee, V. Kelly, C. Peedell, M. Snee,
- SOCCAR: A randomised phase II trial comparing sequential versus concurrent chemotherapy and radical hypofractionated radiotherapy in patients with inoperable stage III Non-Small Cell Lung Cancer and good performance status, European Journal of Cancer, Volume 50, Issue 17, 2014, Pages 2939-2949, ISSN 0959-8049, https://doi.org/10.1016/j.ejca.2014.07.009.