VINORELBINE, CISPLATIN & RADIOTHERAPY

Chemo-radiotherapy for unresectable Stage III NSCLC

Drugs/Dosage:

Neo-adjuvant chemotherapy (one cycle only):

Vinorelbine	30mg/m^2	IV	Day 1 and Day 8
Cisplatin	80mg/m^2	IV	Day 1

then

Chemo-radiotherapy (3 cycles):

Vinorelbine	15mg/m^2	IV	Day 1 and Day 8
Cisplatin	75mg/m^2	IV	Day 1

Radiotherapy: All patients to receive 64Gy in 32 fractions (2Gy/#) on weekdays only, over 6½ weeks. Radiotherapy to be given within 6 hours after cisplatin infusion completed

Administration: Vinorelbine diluted in 50ml 0.9% sodium chloride and infused over 5-10 minutes, running concurrently with 0.9% sodium chloride infusion.
Flush the vein afterwards with a further 250ml saline infusion at a free flowing rate.
(On Day 1, if at least 250ml of the cisplatin pre-hydration remains, this may be used as the flush instead)

Cisplatin: 1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgS0_4$ IV over 2 hours
Mannitol 20% 100mls IV over 15 minutes
Cisplatin in 1 litre 0.9% sodium chloride IV over 3 hours
1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgS0_4$ IV over 2 hours
500ml sodium chloride 0.9% IV **or** 500mls – 1 litre water orally over 1 hour.

Frequency: Chemo-radiotherapy: 3 weekly cycle for 3 cycles
1 cycle of vinorelbine & cisplatin chemotherapy to be given neo-adjuvantly, as above, with the chemo-radiotherapy starting 3 weeks later.

Main Toxicities: myelosuppression; neurotoxicity; ototoxicity; alopecia (occasional); constipation; nephrotoxicity; ovarian failure / infertility;
RT side-effects (oesophagitis; mucositis; pneumonitis; skin toxicity)

Anti-emetics: Day 1: highly emetogenic, including aprepitant *(aprepitant not required if carboplatin switch)*
Day 8: mildly emetogenic

Extravasation: vinorelbine is a vesicant

Regular investigations:

FBC	Day 1 and Day 8 (and weekly while on RT)
U&Es	Day 1
Mg^{2+} and Ca^{2+}	Day 1
LFTs	Day 1
EDTA	Prior to 1st cycle

Comments: If EDTA not yet available for patients on Cycle 1, use Cockcroft & Gault formula to predict GFR. Cisplatin dose should be adjusted if necessary on future cycles once EDTA available. EDTA should only be repeated if the result is borderline at the start of treatment or if there is a 30% change in serum creatinine.

Reason for Update: updated advice regarding options for poor renal function	Approved by Consultant: Dr V Ezhil
Version: 6	Approved by Lead Chemotherapy Nurse: S Wills-Percy
Supersedes: Version 5	Date: 23.11.17
Prepared by: S Taylor	Checked by: C Tucker

Check electrolytes – additional supplements of magnesium, calcium or potassium may be required.

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. If the urine output is inadequate, the patient should be assessed and urine output increased by administering 500ml sodium chloride 0.9% IV +/- furosemide 20 -40mg. Furosemide 20 – 40mg po 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.

Dose Modifications

Haematological Toxicity:

Neo-adjuvant cycle:

Day 1: Proceed if neutrophils ≥ 1.5 x 10^9/l and platelets ≥ 100 x 10^9/l.

Day 8: **Omit** the Day 8 vinorelbine (do NOT delay) if neutrophils < 1.0 x 10^9/l or platelets < 100 x 10^9/l

Chemo-radiotherapy: (Day 1* and Day 8):

*****_As this is potentially curative, it is important that chemotherapy doses are selected using an FBC within 24 hours of Day 1 or Day 8._
Do not **reduce** any doses according to an FBC from a Thursday or Friday clinic pre Day 1; if FBC is low, it must be re-checked on Day 1 and then doses prescribed accordingly

Neutrophils ≥ 1.5 x 10^9/l and Platelets > 75 x 10^9/l	Proceed with full dose treatment
Neutrophils 1.0 – 1.4 x 10^9/l and / or Platelets 50 - 75 x 10^9/l	Give 50% doses of vinorelbine and cisplatin *(if switched to carboplatin, reduce to carboplatin AUC 4).* Consider G-CSF prophylaxis with further cycles if appropriate.
Neutrophils < 1.0 x 10^9/l or Platelets < 50 x 10^9/l	Omit cisplatin (or carbo) and vinorelbine doses. Continue with radiotherapy. Consider G-CSF prophylaxis with further cycles.

Non-haematological Toxicities:

If, after one or more cycles, it is required to discontinue cisplatin due to toxicity (such as deterioration in renal function or development of tinnitus), options are:

a) stop all chemotherapy and continue with RT alone

or

b) switch from cisplatin to carboplatin AUC 5, administered in 250ml 5% glucose over 30 - 60 minutes on Day 1 of each cycle. There is no requirement for pre- or post-hydration, nor fluid balance/urine monitoring.

Neurotoxicity:

For Grade 2 neurotoxicity, give 50% vinorelbine and cisplatin doses.
Chemotherapy should be omitted in the event of any Grade 3 - 4 neurotoxicity. The decision to re-introduce chemotherapy if symptoms resolve should be made by a Consultant only. Seek further advice if the patient reports symptoms indicative of ototoxicity (tinnitus, deafness).

Renal Impairment: NB. Cisplatin is both eliminated primarily (> 90%) in the urine and is itself nephrotoxic.

GFR (ml/min)	Cisplatin Dose
≥ 60	Give 100%
45 – 59	Give 75%
< 45	Cisplatin contra-indicated Options are: a) Substitute with carboplatin AUC 5, administered in 250ml 5% glucose over 30 – 60 minutes. It may be given according to this protocol, with however no requirement for pre- or post-hydration, nor fluid balance/urine monitoring or b) consider the weekly paclitaxel & carboplatin CRT regimen (only if not yet started treatment)

Hepatic Impairment: If ALT/AST > 5 x ULN and / or bilirubin > 2 x ULN, it is suggested that the vinorelbine dose be reduced by 33% and haematological toxicity closely followed up.

References:

Hirose, T et al; Cancer Chemother Pharmacol 2006; 58 (3): 361 – 367
Vokes, E et al; JCO 2002; 20 (20): 4191 – 4198
Zatloukal, P et al; Lung Cancer 2004; 46 (1): 87 – 98
Ishida, K et al; Mol Clin Oncol 2014; 2 (3): 405 – 410 (carbo)