SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Alternating Lomustine Cyclophosphamide Vincristine and Cyclophosphamide Mesna Vincristine Adjuvant treatment of Medulloblastoma

Medulloblastoma maintenance chemotherapy post radiotherapy

PROTOCOL REF: MPHALCVCMVM
(Version No.:1.1)

Approved for use in:

Maintenance adjuvant treatment of newly diagnosed standard risk medulloblastoma following chemo-radiotherapy

Dosage:

Maintenance chemotherapy beginning 6 weeks after radiotherapy for 8 alternating cycles.

Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8
V – L - Cis		V – L – Cis		V – L - Cis		V – L - Cis	
	V – Cyclo - M		V – Cyclo – M		V – Cyclo - M		V – Cyclo - M
6 weeks	3 weeks	6 weeks	3 weeks	6 weeks	3 weeks	6 weeks	3 weeks

V – L – Cis: Vincristine, lomustine & cisplatin (**42-day cycle)**
V – Cyclo – M: Vincristine, cyclophosphamide & mesna **(21-day cycle)**

Alternating cycles for a total of 8 cycles

Please note can be given in an alternative order beginning with V-cyclo M as cycle 1 and V – L – Cis as cycle 2 as per practice at Alder Hey.

Vincristine Lomustine Cisplatin (6 week cycle) - C1/C3/C5/C7			
Drug	**Dose**	**Frequency**	**Route**
Vincristine	**2mg**	Day 1, 8 & 15 of **6 week cycle**	IV
Lomustine	**75mg/m^2**	Day 1 of **6 week cycle**	Oral
Cisplatin	**70mg/m^2**	Day 1 of **6 week cycle**	IV

Vincristine Cyclophosphamide + Mesna (3 week cycle) – C2/C4/C6/C8			
Drug	**Dose**	**Frequency**	**Route**
Vincristine	**2mg**	Day 1 of a **3 week** cycle	IV
Mesna (pre)	**500mg/m^2**	Day 1 & Day 2 of a **3 week** cycle	IV
Cyclophosphamide + Mesna	**1000mg/m^2 + 1000mg/m^2**		
Mesna (post)	**1000mg/m^2**		

Counselling Points:

Lomustine - available as a 40mg capsule and should be taken on an empty stomach with water.

Pregnancy

Animal studies have shown vincristine, cyclophosphamide, lomustine and cisplatin cause teratogenicity and other reproductive toxicity.

Lomustine has the potential to cause irreversible infertility in men. Sperm banking may be considered prior to treatment.

Emetogenic risk

Vincristine – Minimally emetogenic.

Cyclophosphamide – Moderately emetogenic

Lomustine – Moderately emetogenic

Cisplatin – Highly emetogenic

Supportive treatments:

- Aprepitant 125mg prior to chemotherapy then 80mg daily on day 2 and day 3.
- Ondansetron 8mg twice daily when required.
- Domperidone 10mg up to THREE times a day when required.
- Filgrastim 30million units or 48million units subcutaneously daily for 7 days (see administration section for specific details).

Patients should not receive steroid therapy, e.g. dexamethasone, during radiotherapy and chemotherapy, if possible. If symptoms of raised intra- cranial pressure develop during treatment the cause, e.g. hydrocephalus, should be actively sought. Steroids should be used as a short-term measure prior to definitive treatment of the raised pressure. Use of dexamethasone should be documented prospectively.

Extravasation risk:

Vincristine – vesicant

Cyclophosphamide - irritant

Cisplatin – Irritant

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

Dosing in renal and hepatic impairment:

Renal	
Vincristine	
Metabolism and elimination is primarily hepatic therefore no dose adjustments are required in renal impairment	
Cyclophosphamide	
CrCL ≥30ml/min (Cockcroft-Gault)	No adjustment required
10ml/min > CrCL > 30ml/min (Cockcroft-Gault)	75% of original dose
CrCL < 10ml/min (Cockcroft-Gault)	Not recommended
Lomustine	
CrCL ≥50ml/min (Cockcroft-Gault)	No adjustment required
30ml/min ≥ CrCL > 50ml/min (Cockcroft-Gault)	75% of original dose
CrCL <30ml/min (Cockcroft-Gault)	Not recommended
Cisplatin	
CrCL ≥50ml/min (Cockcroft-Gault)	No adjustment required
40ml/min ≥ CrCL > 50ml/min (Cockcroft-Gault)	75% of original dose
CrCL <40ml/min (Cockcroft-Gault)	Not recommended

Hepatic	
Vincristine	
Metabolism and elimination is primarily hepatic therefore increased toxicity may be experienced in hepatic impairment. Bilirubin >51 µmol/L – 50% of original dose	
Cyclophosphamide	
*Mild to moderate	No adjustment required
**Severe	Not recommended – may reduce efficacy
Lomustine	
*Mild to moderate	No adjustment required
**Severe	Not recommended
Cisplatin	
No adjustment required	

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Mild	Bilirubin >1.0-1.5 x ULN **OR** AST > ULN
Moderate	Bilirubin 1.5-3 x ULN
Severe	Bilirubin >3.0 x ULN
As classified by Organ Dysfunction Working Group:	

Treatment schedule:

Vincristine / Lomustine / Cisplatin – C1/C3/C5/C7

Day	Drug	Dose	Route	Diluent and rate
1	**Aprepitant**	**125mg**	**PO**	60 mins before chemotherapy
	Ondansetron	**24mg**	**PO**	30 mins before chemotherapy
	Lomustine	**75mg/m^2**	**PO**	
	Vincristine	**2mg**	**IV**	50mL Sodium Chloride 0.9% over 10mins
	Furosemide oral tablets	**20mg**	**PO**	
	Sodium Chloride 0.9% 1000mL With 20mmol Potassium Chloride		**IV over 90 minutes**	
	Measure urine output volume and record **If urine output averages 100mL/hour over previous 3 hours then proceed with cisplatin infusion** **If urine output is less than 100mL/hour the patient should be assessed and further 500mL sodium chloride 0.9% given IV over 30 minutes** **If urine output still not adequate contact the urology team**			
	Cisplatin	**70mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 90 minutes
	Sodium Chloride 0.9% 1000mL With 20mmol Potassium Chloride		**IV over 90 minutes**	
2	**Ondansetron**	**8mg**	**PO**	Twice daily for 3 days from Day 2
	Filgrastim	**30 million units / 48 million units**	**SC**	By subcutaneous injection daily for 7 days from Day 2 **(NOT on day of vincristine)**
8	**Vincristine**	**2mg**	**IV**	50mL Sodium Chloride 0.9% over 10mins
15	**Vincristine**	**2mg**	**IV**	50mL Sodium Chloride 0.9% over 10mins

Vincristine / Cyclophosphamide + Mesna – C2/C4/C6/C8

Day	Drug	Dosage	Route	Diluent and Rate
1	**Ondansetron** **30 minutes before chemotherapy**	**16mg**	**PO**	
	Vincristine	**2mg**	**IV**	50mL Sodium Chloride 0.9% over 10mins
	Mesna	**500mg/m^2**	**IV**	In 500mL sodium chloride 0.9% over 1 hour
	Cyclophosphamide + mesna	**1000mg/m^2 + 1000mg/m^2**	**IV**	In 1000mL sodium chloride 0.9% over 3 hours
	Mesna	**1000mg/m^2**	**IV**	In 1000mL sodium chloride over 8 hours
2	**Ondansetron**	**16mg**	**PO**	24 hours after day 1 dose
	Mesna	**500mg/m^2**	**IV**	In 500mL sodium chloride 0.9% over 1 hour
	Cyclophosphamide + mesna	**1000mg/m^2 + 1000mg/m^2**	**IV**	In 1000mL sodium chloride 0.9% over 3 hours
	Mesna	**1000mg/m^2**	**IV**	In 1000mL sodium chloride over 8 hours
3	**Ondansetron**	**8mg**	**PO**	Twice daily for 3 days from Day 3
	Filgrastim	**30million units or 48million units**	**SC**	By subcutaneous injection daily for 7 days from Day 3

Main toxicities:

Nausea and vomiting, anaemia, thrombocytopenia, neutropenia, lethargy.

Vincristine
Neuropathy, constipation, arthralgia, myalgia, polyuria, dysuria, urinary retention, hypertension, hypotension.
Cyclophosphamide
Alopecia, mucositis, diarrhoea Urotoxicity can occur with short-term and long-term use of cyclophosphamide. Hemorrhagic cystitis, pyelitis, ureteritis, and haematuria. Additional mesna can be given if required.
Lomustine
Disorientation, mucositis, pulmonary fibrosis, alopecia, renal injury/failure, increased bilirubin, increased transaminases.
Cisplatin
Arrhythmia, bradycardia, tachycardia, nephrotoxicity, otoxicity, loss of fertility, anaphylactic reactions

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Ongoing
Informed Consent	X						
Clinical Assessment with neurological examination	X	X	X	X	X	X	
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	Every cycle
FBC, U&E, LFTs, bone profile, magnesium (to be checked pre & post chemotherapy to identify nadir counts)	X	X	X	X	X	X	Every cycle
CrCl (Cockcroft and Gault)	X	X	X	X	X	X	Every cycle
CT scan	X						Every 6 months/if clinically indicated
ECG							If clinically indicated
Full observations	X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	Every cycle
Height recorded	X						
Pregnancy test	X						
MRI spine to include visualization of the end of the dural sac	x						
Audiology – pure tone audiometry if possible. If not possible, normal acoustic emissions are acceptable if no history of hearing deficit	x						

During treatment and for 12 months after, appropriate measures must be taken to avoid pregnancy by women of childbearing age. For men effective contraception should be used during treatment and for 6 months after.

Dose Modifications and Toxicity Management:

Haematological toxicity:

Prior to Vincristine, Lomustine & Cisplatin (6 week cycle) – C1/C3/C5/C7:

Proceed on Day 1 if -

WBC ≥ 2.0 x 10^9/L	ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

WBC ≤ 2.0 x 10^9/L	ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L
If platelet /WBC recovery is delayed more than 2 weeks then omit lomustine for next cycle and reduce lomustine to 50mg/m^2 in all subsequent cycles. For any further episodes of delayed count recovery, omit lomustine for next and all subsequent cycles (give full dose cisplatin)		

If the nadir count (after each cycle) meets the criteria below then dose reduce lomustine to 50mg/m^2 in next and all subsequent cycles and consider additional CSF next course -

WBC <2.0 x 10^9/L	ANC <0.5 x 10^9/L	Plt <30 x 10^9/L	Episode of febrile neutropenia
If further episodes with GCSF then reduce cisplatin to 50mg/m^2 in the next and all subsequent cycles			

Prior to Vincristine, Cyclophosphamide & Mesna – C2/C4/C6/C8

Proceed on Day 1 if -

ANC ≥ 1.0 x 10^9/L	Plt ≥ 80 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 80 x 10^9/L

If the nadir count (after each cycle) meets the criteria below then dose reduce lomustine to 50mg/m^2 in next and all subsequent cycles and consider additional GCSF next course

WBC <2.0 x 10^9/L	ANC <0.5 x 10^9/L	Plt <30 x 10^9/L	Episode of febrile neutropenia
If further episodes with GCSF then reduce cisplatin to 50mg/m^2 in the next and all subsequent cycles			

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non – Haematological toxicity:

Nephrotoxicity	
Creatinine >1.5 ULN or CrCL <60mL/min	Delay chemotherapy for 1 week
CrCL 41 to 50 mL/min/1.73m^2	Delay chemotherapy until CrCL returns to baseline. Reduce subsequent doses to 75%.
eGFR ≤ 40 mL/min/1.73m^2	Consider switch to carboplatin.
Neurotoxicity	
< Grade 1 or grade 2 persisting < 7 days	Continue vincristine at full dose
Grade 2 persisting > 7 days	Discontinue vincristine
Constipation / Ileus	
Ileus ≥ grade 2 lasting ≤ 7 days	Omit vincristine from next cycle. Discuss with consultant whether to re-start
Ileus ≥ grade 2 lasting > 7 days	Discontinue vincristine
Ototoxicity	
Grade 2	Substitute cisplatin for carboplatin
Grade 3 or 4	Omit platinum
Haematuria	
Microscopic during cyclophosphamide infusion	Give additional bolus doses of Mesna then a continuous infusion at double dose
Gross haematuria	Omit Day 2 cyclophosphamide. Give cyclophosphamide at 50% of the original dose for the next cycle. If well tolerated, consider reescalation.

References:

Jorgensen M, Pizer B, Horan G. Interim guidelines for Standard Risk Medulloblastoma For children from 3 years of age. Page 16. Children's Cancer and Leukaemia Group January 2019.

Packer RJ, Gajjar A, Vezine G et al. Phase III Study of Craniospinal Radiation Therapy Followed by Adjuvant Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma. Journal of Clinical Oncology 24, no. 25 (September 01, 2006) 4202-4208.

Martin MA, Raabe E, Cohen KJ. Management of Pediatric and Adult Patients with Medulloblastoma. Curr Treat Options Oncol. 2014 December ; 15(4): 581–594.

Greenberg HS, Chamberlain MC, Glantz MJ, Wang S. Adult medulloblastoma: multiagent chemotherapy. Neuro Oncol 2001 Jan;3(1):29-34.

Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.

Vincristine Sulphate 1 mg/ml Injection (5 mg/5 ml). Summary of Product Characteristics. Hospira UK Ltd. Available via https://www.medicines.org.uk/emc (last updated 01/12/21).

Cyclophosphamide 500 mg Powder for Solution for Injection or Infusion. Sandoz Limited. Available via https://www.medicines.org.uk/emc (last updated 10/03/21).

Lomustine "medac" 40 mg. Summary of Product Characteristics. Medac GmbH. Available via https://www.medicines.org.uk/emc (last updated 01/04/20).

Cisplatin 1 mg/ml Sterile Concentrate, Summary of Product Characteristics. Hospira UK Ltd. Available via https://www.medicines.org.uk/emc (last updated 01/06/21).

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