Systemic Anti Cancer Treatment Protocol

POMB ACE
Cisplatin Vincristine Methotrexate Bleomycin –
and
Dactinomycin Cyclophosphamide Etoposide –

PROTOCOL REF: MPHAPOACGC
(Version No: 1.1)

Approved for use in:

Germ cell tumours with CNS involvement

Dosage:

Cycles are given every 14 days in the following order to maximum of 7 cycles followed by review

POMB – Cisplatin Vincristine Methotrexate Bleomycin C1/C2/C4/C6

Drug	Dosage	Route	Frequency
Vincristine	2mg flat dose	IV	Day 1
Methotrexate	1000mg/m^2	IV	Day 1
Bleomycin	15,000 units flat dose	IV	Days 2 and 3
Cisplatin	120mg/m^2	IV	Day 4

ACE – Dactinomycin Cyclophosphamide Etoposide C3/C5/C7

Drug	Dosage	Route	Frequency
Etoposide	100mg/m^2	IV	Days 1, 2 and 3
Dactinomycin	500 micrograms	IV	Days 1, 2 and 3
Cyclophosphamide	500mg/m^2	IV	Day 3

P	Cisplatin
O	Vincristine
M	Methotrexate
B	Bleomycin
A	Dactinomycin

Cycle Number	Treatment Given
1	POMB
2	POMB
3	ACE
4	POMB
5	ACE

C	Cyclophosphamide
E	Etoposide

6	POMB
7	ACE

Supportive treatments:

Aprepitant 125mg day 4 prior to cisplatin with 80mg on days 5 and 6

Domperidone 10mg oral tablets, up to 3 times a day or as required

Dexamethasone 4mg twice daily for 3 days following ACE regimen

Extravasation risk:

Refer to local policy:

Methotrexate – non vesicant

Bleomycin and cyclophosphamide – non vesicant

Cisplatin and etoposide - irritants

Dactinomycin and vincristine - vesicant

Administration:

POMB – Cisplatin Vincristine Methotrexate Bleomycin C1/C2/C4/C6

Day1 – Chemotherapy + Folinic Acid Rescue + Fluid Rescue

Please refer to POMB ACE FOLINIC ACID prescribing guide for guidance on prescribing on Meditech.

Day	Drug	Dosage	Route	Diluent and Rate
T -24hrs	Sodium bicarbonate tablets 3000mg		PO	6 x 500mg tablets
T -20hrs	Sodium bicarbonate tablets 3000mg		PO	6 x 500mg tablets
T -16hrs	Sodium bicarbonate tablets 3000mg		PO	6 x 500mg tablets
	Patient admitted Measure urine pH Take UECs Calculate creatinine clearance – must be above 70mL/min			
T-12hrs	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Infuse over 4 hours

Day	Drug	Dosage	Route	Diluent and Rate
T-8hrs	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Infuse over 4 hours
T-4hrs	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Infuse over 4 hours
T-½hr	Ondansetron tablets 16mg Dexamethasone 12mg		PO PO	2 x 8mg tablets 6 x 2mg tablets
T-½hr	**Vincristine**	**2mg**	IV	In 50mL sodium chloride 0.9% over 15 minutes
T0	**Sodium bicarbonate infusion to run concurrently with methotrexate via a separate lumen**			
T0	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Infuse over 6 hours
T0	Measure urine pH. Commence methotrexate infusion if urine pH ≥ 8 If urine pH <8 give additional oral dose of 3g sodium bicarbonate and continue with further intravenous infusions until pH ≥ 8			
T0	**Methotrexate** in 1000ml sodium chloride 0.9% + concurrent hydration	**1000 mg/ m^2**	IV	*Record the time administration commenced. And stop infusion at 24 hours from start time*
T+6hrs	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Infuse over 6 hours
T +12hrs	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Infuse over 6 hours
T +18hrs	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Infuse over 6 hours
T +24hrs	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Infuse over 6 hours
T +24hrs	Day 2 chemotherapy to commence see below for details			
T +24hrs Then repeat every 24 hours	Take first Methotrexate level Then repeat 24 hourly until a total of 4 levels have been taken.			Repeated every 24 hours
T +30hrs	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Infuse over 6 hours
T +36hrs **Then repeated 6 hourly**	Commence Folinic acid rescue Folinic acid 15mg in 100ml NaCL0.9% over 30 mins		IV	Repeated every 6 hours for 12 doses which takes 72 hours

Day	Drug	Dosage	Route	Diluent and Rate
T +36hrs **Then continuous**	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9% **Rate 1000ml every 8hrs** **STOP when folinic acid course completed.**		IV	Back to back Can change bags every 6hrs to coincide with folinic acid administration Waste excess fluid
T+96hrs	Final methotrexate level. (Level 4 of 4). **If level >0.1 patient will need extended folinic acid / fluid course. Please contact the clinical team.**			
T+102hrs	Last Folinic acid 15mg in 100ml NaCL0.9% over 30 mins **begins** (infusion 12/12) 70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Typically occurs in early hours of D6 Once complete patient will have received 72hrs of fluids and folininic acid

POMB Day 2 – Chemotherapy

Please refer to day 1 for info ongoing IV hydration / folic acid rescue / Methotraxate levels

D2	Hydrocortisone 30 mins prior to bleomycin	100mg	IV	Slow IV bolus over 5 minutes
D2	**Bleomycin**	**15,000 units**	IV	500mL sodium chloride 0.9% over 12 hours

POMB Day 3 – Chemotherapy

Please refer to day 1 for info ongoing IV hydration / folic acid rescue / Methotraxate levels

D3	Hydrocortisone 30 mins prior to bleomycin	100mg	IV	Slow IV bolus over 5 minutes
D3	**Bleomycin**	**15,000 units**	IV	500mL sodium chloride 0.9% over 12 hours

POMB Day 4 – Chemotherapy

Please refer to day 1 for info ongoing IV hydration / folic acid rescue / Methotraxate levels

D4	**Aprepitant** Immediately prior to hydration	**125mg**	**PO**	
D4	**Ondansetron** Immediately prior to hydration	**16mg**	**IV**	
D4	**Dexamethasone** Immediately prior to hydration	**12mg**	**IV**	
D4	Sodium Chloride 0.9% 1000mL with 20mmol Potassium Chloride and 10mmol Magnesium Sulphate	1000mL	**IV**	Over 2 hours
D4	**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 medical team			
D4	**Cisplatin**	**120mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 12 hours
D4	Sodium Chloride 0.9% 1000mL with 20mmol Potassium Chloride and 10mmol Magnesium Sulphate	1000mL	**IV**	Over 4 hours
D4	Sodium Chloride 0.9% 1000mL	1000mL	**IV**	Over 4 hours

Notes:

Bleomycin (see also toxicity management)

Ensure Hydrocortisone given prior to bleomycin to prevent rigors and any acute hypersensitivity reactions

Bleomycin infusion can run concurrently with sodium bicarbonate down a separate lumen on Day 2

Pulmonary toxicity is much more common at cumulative doses > 300,000 units.

Bleomycin will be omitted from this regimen if the patient has had prior BEP chemotherapy

Cisplatin

Ensure adequate hydration pre and post cisplatin

Check and correct electrolytes, Mg^{2+}, Ca^{2+}, K^{+} before starting cisplatin and check them each cycle throughout treatment.

Encourage oral hydration throughout treatment e.g. one glass of water per hour.

Do not start Cisplatin infusion unless urine output is at least 100mL/hour. Give 20 to 40mg furosemide orally if there is a positive fluid balance of 1.5 litres, weight gain of 1.5kg or symptoms of fluid overload.

The patient should be asked to drink 2 litres of fluid over 24 hours after the infusion and should contact the unit immediately if unable to do so for any reason.

Methotrexate

Do not give methotrexate if renal function is abnormal (see below)

Note the time the methotrexate infusion is started

Ensure adequate fluid with electrolytes and bicarbonate is given to maintain urine output and alkalinity. Note that transient rises in liver transaminases are expected with high dose methotrexate and are not an indication for dose modification – see toxicities below

ACE – Cycles 3, 5 and 7

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone	8mg	Oral	30 minutes before chemotherapy
1	Ondansetron	16mg	Oral	30 minutes before chemotherapy
1	**Dactinomycin**	**500micrograms**	IV	100mL sodium chloride 0.9% over 30 minutes
1	**Etoposide**	**100mg/m^2**	IV	500mL sodium chloride 0.9% over 60 minutes
2	Dexamethasone	8mg	Oral	30 minutes before chemotherapy
2	Ondansetron	16mg	Oral	30 minutes before chemotherapy
2	**Dactinomycin**	**500micrograms**	IV	100mL sodium chloride 0.9% over 30 minutes
2	**Etoposide**	**100mg/m^2**	IV	500mL sodium chloride 0.9% over 60 minutes
3	Dexamethasone	8mg	Oral	30 minutes before chemotherapy
3	Ondansetron	16mg	Oral	30 minutes before chemotherapy
3	**Dactinomycin**	**500micrograms**	IV	100mL sodium chloride 0.9% over 30 minutes
3	**Etoposide**	**100mg/m^2**	IV	500mL sodium chloride 0.9% over 60 minutes
3	**Cyclophosphamide**	**500mg/m^2**	IV	Over 30 minutes

Filgrastim dose:

For patients under 70kg: 300 micrograms subcutaneous injection daily for 7 days

For patients 70kg and above: 480 micrograms subcutaneous injection daily for 7 days

Main Toxicities:

Myelosuppression, nephrotoxicity, ototoxicity, mucositis, neurotoxicity, alopecia, skin changes, infertility, pulmonary toxicity, rigors (during bleomycin – see notes)

Investigations:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Comments
Medical Assessment	X		X		X	Alternate cycles
Nursing Assessment		X	X	X	X	
FBC		X	X	X	X	Do not delay or omit D15 bleomycin due to low counts.
U&E & LFT		X	X	X	X	Check electrolytes each cycle throughout treatment
Serum Creatinine	X	X	X	X	X	Check each cycle throughout treatment
CrCl (Cockroft and Gault)		X	X	X	X	Check each cycle throughout treatment
Ca2+, Mg2+		X	X	X	X	Repeat within the cycle if needed
LDH	X		X	X	X	
AFP, βHCG	X		X	X	X	
Chest X-Ray	X		X		X	Before each cycle containing bleomycin
CT scan	X					At end of treatment
Pulmonary function tests	X					If clinically indicated
Informed Consent	X					
Blood pressure measurement	X	X	X	X	X	
PS recorded	X	X	X	X	X	Every administration
Toxicities documented		X	X	X	X	Every administration
Weight recorded	X	X	X	X	X	Every cycle
Height recorded	X					
Pregnancy Test	X					

During treatment and for a minimum of the following 6 months, appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes.

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if:-

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

If patient does not reach these parameters, discuss with consultant.

Non-haematological toxicity

Renal

Methotrexate

Renal function	Action
GFR < 70mL/min/1.73m^2	Delay one week, if no improvement omit methotrexate and proceed to next possible cycle. Resume Methotrexate when GFR > 70mL/min/1.73m^2

Cisplatin is eliminated primarily (>90%) in the urine and is itself nephrotoxic. If there is any significant renal toxicity discuss with consultant before proceeding.
Calculate CrCl before the start of treatment using Serum Creatinine and Cockroft and Gault. If the result is borderline consider EDTA clearance. Recalculate CrCl using Cockroft and Gault every cycle and consider EDTA if serum creatinine varies by >30% from baseline.

CrCl (mL/min)	Cisplatin dose
Above 50	100% dose
40 to 50	75% dose
Below 40	Do not give, discuss with consultant consider carboplatin
	Bleomycin dose
Above 50	100% dose
10 to 50	75% dose
	Etoposide dose
Above 50	100% dose
15 to 50	75% dose
Below 15	50% dose

<table>
<tr><td>Hepatic</td><td>
Methotrexate
<table>
<tr><td>Abnormal LFT not methotrexate induced</td><td>Delay one week – Give if ALT < 10 x ULN</td></tr>
<tr><td>Elevated LFT probably methotrexate induced (up to 3 weeks after)</td><td>No dose alterations expected</td></tr>
<tr><td>Bilirubin > 1.25 x ULN persistent for > 3 weeks</td><td>Discontinue Methotrexate</td></tr>
</table>
Dactinomycin
No specific guidance but consider dose reductions of dactinomycin in severe hepatic dysfunction
Etoposide
Creatinine clearance is the strongest predictor of etoposide clearance. There is conflicting advice about the need for dose adjustment with hepatic impairment. Use table below but discuss with consultant need for any adjustment
<table>
<tr><th>Bilirubin (micromol/L)</th><th>AST (units/L)</th><th>Etoposide Dose</th></tr>
<tr><td>26 to 51
OR</td><td>60 - 180</td><td>50% dose</td></tr>
<tr><td>Above 51
OR</td><td>Above 180</td><td>Clinical decision</td></tr>
</table>
</td></tr>
<tr><td>Pulmonary</td><td>Bleomycin may cause severe and life threatening pulmonary toxicity.
Toxicity is associated with cumulative doses over 300,000 units and patients of older age as well as poor renal function, advanced disease, smoking history. Bleomycin must be discontinued permanently if signs of pulmonary toxicity occur but this is a consultant decision only. Discuss with consultant if symptoms occur e.g. dyspnea, abnormal chest X-Ray or decreased pulmonary function. Note that concomitant oxygen or radiation therapy can influence the risk of developing pulmonary toxicity. Use room air for pulmonary function tests. Avoid oxygen concentrations above 30-40%.</td></tr>
<tr><td>GI toxicity</td><td>Cisplatin induced nausea and vomiting may be severe. Uncontrolled vomiting may exacerbate cisplatin induced fluid and electrolyte imbalance. Follow antiemetic policy rigorously and monitor fluids and electrolytes closely if severe vomiting occurs. Note that electrolyte disturbance due to cisplatin may be a long term manifestation due to renal tubular dysfunction. Check electrolytes, longer term supplementation with magnesium, potassium or calcium may be required.
Methotrexate may also be a causative agent</td></tr>
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Acute Hypersensitivity and fever	**Bleomycin** Hypersensitivity is rare but not unknown and severe when it occurs. Stop infusion and follow trust anaphylaxis policy. Half of patients will have a febrile reaction to bleomycin within 48 hours. Hydrocortisone should prevent this and paracetamol can be used to treat. **Cisplatin and Etoposide** Anaphylactic like reactions have been reported. These commonly include facial oedema, bronchoconstriction, tachycardia, hypotension. Follow trust anaphylactic policy. Discuss next cycle with consultant before proceeding
Skin	50% of patients will develop a rash with bleomycin – this is normal. Severe skin lesions may also occur. Discuss with consultant. **Decision to stop is consultant only.**
Mucositis	Discuss – delay until recovery, note that concomitant radiotherapy and high cumulative doses of bleomycin are risk factors If considered methotrexate induced, consider increasing calcium folinate rescue doses.
Neurotoxicity	Seek advice if patient displays symptoms of neuro- or ototoxicity

References:

Husband, D. and Green, J. (1992). chemotherapy in non-seminomatous germ cell tumours: Outcome and importance of dose intensity. *European Journal of Cancer*, 28(1), pp.86-91.

Hitchins, R., Newlands, E., Smith, D., Begent, R., Rustin, G. and Bagshawe, K. (1989). Long-term outcome in patients with germ cell tumours treated with POMB/ACE chemotherapy: comparison of commonly used classification systems of good and poor prognosis. *British Journal of Cancer*, 59(2), pp.236-242.