Systemic Anti Cancer Treatment Protocol

PAM AM
Cisplatin Doxorubicin Methotrexate
then
Doxorubicin Methotrexate

PROTOCOL REF: MPHACIDOME
(Version No. 1.1)

Approved for use in:

Osteosarcoma, resectable – methotrexate to be used with caution in patients over 40 years High grade bone sarcomas

Leiomyosarcoma of bone

Dosage and Schedule: Neo-adjuvant / postoperative schedule

	Cycle – PAM					Cycle 2 – PAM					Surgery	Cycle 3 – PAM				
	PA			M	M	PA			M	M		PA			M	M
Day	D1			D22	D29	D1			D22	D29		D1			D22	D29
Wk	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	5 Weeks					5 Weeks						5 Weeks				

	Cycle 4 – PAM					Cycle 5 - AM				Cycle 6 - AM			
	PA			M	M	A		M	M	A		M	M
Day	D1			D22	D29	D1		D15	D22	D1		D15	D22
Wk	17	18	19	20	21	22	23	24	25	26	27	28	29
	5 Weeks					4 Weeks				4 Weeks			

P – Cisplatin
A – Doxorubicin
M - Methotrexate

PAM – Cisplatin Doxorubicin Methotrexate C1- C4

Drug	Dosage	Route	Frequency
Cisplatin	60mg/m^2 days 1 and 2	IV	Every 35 days
Doxorubicin	37.5mg/m^2 days 1 and 2	IV	Every 35 days
Methotrexate	12gram/m^2 days 22, 29	IV	Every 35 days

AM – Doxorubicin Methotrexate C5 + C6

Drug	Dosage	Route	Frequency
Doxorubicin	37.5mg/m^2 days 1 and 2	IV	Every 28 days
Methotrexate	12gram/m^2 days 15, 22	IV	Every 28 days

Supportive treatments:

Anti-emetic risk

High with Cisplatin and

High with Methotrexate

Cisplatin Days

Pre-Meds

Aprepitant PO – 125mg STAT then 80mg on D2 + D3

Ondansetron PO – 24mg STAT then 24mg on D2

Dexamethasone PO – 12mg STAT

Take Home

Dexamethasone – 4mg BD on D3-D5

Filgrastim – commence on day 3 for 7 days, then review FBC - continue if neuts low

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

Methotrexate Days

Pre-Meds

Ondansetron PO – 16mg STAT

Dexamethasone PO – 12mg STAT

Take Home

Dexamethasone – 4mg BD on D3-D5

Filgrastim – commence on day 3 for 7 days, then review FBC - continue if neuts low

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

Extravasation risk:

Cisplatin – Irritant

Doxorubicin – vesicant; see trust / network protocol specific treatment may apply

Administration: (PA) Cisplatin Doxorubicin – D1 + D2 of C1-C4

Day	Drug	Dosage	Route	Diluent and Rate
1	Aprepitant 30 mins before chemotherapy	125mg	PO	
1	Ondansetron 30 mins before chemotherapy	24mg	PO	
1	Dexamethasone 30 mins before chemotherapy	12mg	PO	
1	**Doxorubicin**	**37.5mg/m^2**	IV	100mL sodium chloride 0.9% over 24 hours
1	Furosemide	20mg	PO	
1	Sodium chloride 0.9% 1000mL with 20mmol potassium chloride	1000mL	IV	Infuse over 90 minutes
1	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			
1	**Cisplatin**	**60mg/m^2**	IV	1000mL sodium chloride 0.9% over 90 minutes
1	Sodium chloride 0.9% 1000mL with 20mmol potassium chloride	1000mL	IV	Infuse over 90 minutes
2	Aprepitant	80mg	PO	To be given 24 hours after the day 1 dose
2	Ondansetron	24mg	PO	To be given 24 hours after the day 1 dose
2	Dexamethasone	12mg	PO	To be given 24 hours after the day 1 dose
2	**Doxorubicin**	**37.5mg/m^2**	IV	100ml sodium chloride 0.9% over 24 hours
2	Furosemide	20mg	PO	
2	Sodium chloride 0.9% 1000mL with 20mmol potassium chloride	1000mL	IV	Infusion over 90 minutes
2	Monitor urine output – see day 1			
2	**Cisplatin**	**60mg/m^2**	IV	1000mL sodium chloride 0.9% over 90 minutes
2	Sodium Chloride 0.9% 1000mL with 20mmol potassium chloride	1000ml	IV	Infusion over 90 minutes
3	Aprepitant	80mg	PO	To be given 24 hours after day 2 dose
3 to 5	Dexamethasone	4mg	PO	Twice daily for 3 days
3 to 9	Filgrastim	30 or 48MU	SC	To be injected daily for 7 days, then repeat FBC

Administration: (A) Doxorubicin on D1 of cycles 5 + 6

Day	Drug	Dosage	Route	Diluent and Rate
1	Ondansetron 30 mins before chemotherapy	24mg	PO	
1	Dexamethasone 30 mins before chemotherapy	12mg	PO	
1	**Doxorubicin**	**37.5mg/m^2**	IV	100mL sodium chloride 0.9% over 24 hours
2	Ondansetron	24mg	PO	To be given 24 hours after the day 1 dose
2	Dexamethasone	12mg	PO	To be given 24 hours after the day 1 dose
2	**Doxorubicin**	**37.5mg/m^2**	IV	100ml sodium chloride 0.9% over 24 hours
3 to 9	Filgrastim	30 or 48MU	SC	To be injected daily for 7 days, then repeat FBC

Administration: (M) High Dose Methotrexate on D22 + D29 of PAM D15+ D22 of AM

Calculate creatinine clearance – must be above 70mL/min prior to methotrexate. Measure urine pH and commence intravenous fluids, starting 12 hours prior to methotrexate administration

Time	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
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

Time	Drug	Dosage	Route	Diluent and Rate
T0	Measure urine pH pH ≥ 8 = Commence methotrexate infusion if urine pH <8 = administer additional oral dose of 3g sodium bicarbonate and continue with further intravenous infusions until pH ≥ 8			
T0	Sodium Bicarbonate	3000mg	PO	To be taken as the methotrexate infusion commences
T0	**Methotrexate** + concurrent hydration	**12 gram/m^2**	IV	Infuse over 4 hours *Record the time administration commenced*
T+4hrs	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Infuse over 4 hours
T+8hrs	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Infuse over 4 hours
T+12hrs	70mL of sodium bicarbonate 8.4% added to 1000mL sodium chloride 0.9%		IV	Infuse over 4 hours
T+16hrs Then continuous	**Continue with intravenous fluids at rate of 3000mL every 24 hours** Back to back REPEATED infusions **until methotrexate level < 0.1 micromol/L** Maintain pH ≥ 8 with intravenous and oral sodium bicarbonate		IV	Give 1000ml sodium chloride 0.9%every 8 hours
T+24hrs	Take Methotrexate level			
T+24hrs	Folinic acid rescue*Commence initial rate folinic acid rescue **<u>exactly 24 hours</u>** after the start of the methotrexate infusion	30mg	IV	See table for doses In 100ml NaCl 0.9% over 30 minutes
T+48hrs T+72hrs T+96hrs etc	Take Methotrexate level Adjust Folinic acid rate as per table Repeat levels every 24hrs and adjust as per table Once level <0.1 micromol/L – stop folinic acid – stop IV fluids – no further levels required			
T+48hrs (Day 3)	Filgrastim	30 or 48MU	SC	To be injected daily for 7 days, then repeat FBC

Folinic acid rescue:
Please refer to PAM FOLINIC ACID prescribing guide for guidance on prescribing on Meditech.

BSA	Methotrexate plasma concentration (micromol/L)			
	<0.1	0.1 – 2.0 INITIAL RATE	2.0 – 20 Escalation Level 1	20 – 100 Escalation Level 2*
≤2.0m^2	Discontinue folinic acid	30mg Q6H	30mg Q3H	100mg/m^2 Q3H
>2.0m^2		45mg Q6H	45mg Q3H	
in 100ml NaCl 0.9% over 30 minutes				

***For any methotrexate level >100 micromol/L inform consultant and pharmacy immediately.**

Filgrastim dose:
For patients < 70kg: 30MU subcutaneous injection daily
For patients' ≥ 70kg: 48MU subcutaneous injection daily

Notes:

Double lumen PICC line is required to administer this regimen

Cisplatin

Ensure adequate hydration pre and post cisplatin

Check and correct electrolytes, Mg2+, Ca2+, K+ before starting cisplatin and check them regularly throughout treatment.

Check patient's weight before and after each cisplatin infusion, maintain a strict fluid balance chart, ensure urine output is adequate.

Doxorubicin

Maximum cumulative dose of doxorubicin: 450 to 550mg/m^2

Perform baseline MUGA if patient is considered at risk of significantly impaired cardiac contractility. If cardiac ejection fraction < 50% discuss

Methotrexate

Do not give methotrexate if renal function is abnormal or in the presence

of a third space Note the time the methotrexate infusion is started
Ensure adequate fluid with electrolytes and bicarbonate is given to maintain urine output and alkalinity. Continue alkalinised fluids until Methotrexate levels are < 0.1micromol/L

Note that transient rises in liver transaminases are expected with high dose methotrexate and are not an indication for dose modification – see toxicities below

Main Toxicities:

Cisplatin:

Mucositis, nausea and vomiting, abdominal pain, alopecia, diarrhoea, fatigue, skin rash, neurotoxicity, allergic reactions, ototoxicity, ovarian failure/infertility.

Doxorubicin:

Myelosuppression, alopecia, mucositis, cardiomyopathy, ovarian failure / infertility

Methotrexate:

Myelosuppression, nephrotoxicity, abdominal pain, diarrhoea, mucositis,

Investigations and treatment plan

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Ongoing
Medical Assessment	X	X	X	X	X	X	X	Every cycle
Nursing Assessment	X	X	X	X	X	X	X	Every cycle
ECHO	X							After cycle 4 or if clinically indicated
FBC	X	X	X	X	X	X	X	Cycles 1 to 4: day 1, 10, 22 and 29 Cycles 5 and 6: day 1, 10, 15 and 22
U&E & LFT*	X	X	X	X	X	X	X	Cycles 1 to 4: day 1, 22 and 29 Cycles 5 and 6: day 1, 15 and 22 **Repeat daily whilst receiving methotrexate**
Mg2+ and Ca2+	X	X	X	X	X	X	X	Every cycle, day 1
CrCl (Cockroft and Gault)	X	X	X	X	X	X	X	Cycles 1 to 4: day 1, 22 and 29 Cycles 5 and 6: day 1, 15 and 22
Urine pH		X	X	X	X	X	X	4 to 6 hourly during methotrexate
CT/MRI scan	X			X				At the end of treatment
Informed Consent	X							
ECG	X							Repeat if clinically indicated
Blood pressure measurement	X	X	X	X	X	X	X	Repeat if clinically indicated
PS recorded	X	X	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	X	X	Every cycle
Audiometry				X				If indicated
Weight recorded	X	X	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Haematological toxicity

For Doxorubicin Cisplatin (AP) and Doxorubicin (with cycles 5 and 6)

Proceed on day 1 if:-

ANC ≥ 0.75 x 10^9/L	Platelets ≥ 75 x 10^9/L

Delay on day 1 if:-

ANC ≤ 0.75 x 10^9/L	Platelets ≤ 75 x 10^9/L

Repeat every 2 to 3 days until above criteria are met.

No previous dose reductions	Treat at full dose
Repeated delays or delay < 7days	Consider adjusting filgrastim regimen
If delays > 7days despite GCSF	Reduce cisplatin by 25%
Febrile neutropenia with or without documented infection Any grade 4 toxicities and consider for grade 3	Further episodes despite filgrastim – reduce cisplatin by 25%

Note: it is essential patients stay on schedule before and after surgery. Discuss any delays or dose alterations with consultant first.

Non-haematological toxicity

Renal

Cisplatin

Renal Function	Action
SrCr > 1.5 x baseline or GFR <70mL/min/1.73m^2	Delay ONE week. If no improvement omit cisplatin and proceed with doxorubicin alone. Resume cisplatin when GFR >70mL/min/1.73m^2

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

Hepatic

Billirubin (micromol/L)	Doxorubicin dose (%)
<21	100
22 to 35	75
36 to 52	50
53 to 86	25
>87	OMIT

Mucositis **Diarrhoea** **Abdominal pain**	Mucositis grade 4 or typhlitis (neutropenic enterocolitis) or repeated grade 3 mucositis Diarrhoea Severe abdominal pain Delay until resolved and reduce subsequent doxorubicin to 60mg/m^2/cycle
Cardiac	LVEF <50% Repeat ECHO or MUGA in one week. If ECHO or MUGA within normal range proceed with chemotherapy If LVEF does not recover, omit all further doxorubicin
Neuropathy	Grade 2 Reduce cisplatin by 25% for all subsequent cycles ≥Grade 3 Omit cisplatin for all future cycles

Methotrexate (M)
Note: no dose reductions will apply

Proceed on day of treatment if:-

ANC ≥ 0.25 x 10^9/L	Platelets ≥ 50 x 10^9/L

Myelosuppression		
	ANC <0.25 x 10^9/L OR WBC <1.0 x 10^9/L OR Plts < 50 x10^9/L	Delay until recovery then proceed with full dose
Renal	If GFR < 70mL/min/1.73m^2 delay until recovery	

Hepatic		
	Abnormal LFT not methotrexate induced	Delay one week – Give if ALT < 10 x ULN
	Elevated LFT probably methotrexate induced (up to 3 weeks after)	No dose alterations expected
	Bilirubin > 1.25 x ULN persistent for > 3 weeks	Discontinue Methotrexate
Mucositis grade 3 or 4 or diarrhoea after methotrexate	Consider calcium folinate rescue adjustment Check for any drugs that might reduce excretion – such as NSAIDs, penicillin	
Diarrhoea or severe abdominal pain		
	Persisting > 1week and present on day 29 of PAM	Omit day 29 Methotrexate and proceed to next cycle of chemotherapy or surgery

References:

Meyers PA, Schwartz CL, Krailo MD, Healey JH, Bernstein ML, Betcher D, et al. Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival--a report from the Children's Oncology Group. J Clin Oncol. 2008;26(4):633-8.

EURAMOS-1, A randomised trial if the European Osteosarcoma Study Group to optimise treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy, v 3.0 July 2011