(MAP) Methotrexate (12000mg/m^2) DOXOrubicin (37.5mg/m^2/day) and CISplatin (60mg/m^2) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Neoadjuvant/Adjuvant therapy of localised or metastatic high grade osteosarcoma of an extremity/axial skeleton (excluding craniofacial sites) -all disease sites amenable to complete surgical resection	C41	00463a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Patients receive induction MAP chemotherapy over 10 weeks as described in treatment table 1 below followed by surgery on week 11.

Post-surgery patients receive chemotherapy with MAP weeks 12 through 29 (see Table 1).

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered

Note:

- **Hydration, alkalinisation and folinic acid therapy required with high dose methotrexate (See Table 1 Below)**

Table 1: Treatment table

Week	Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
Induction MAP (Weeks 1 through10)					
1,6	1,2	[a]DOXOrubicin	37.5mg/m^2	[b]IV push	N/A
1,6	1, 2	[c]CISplatin	60mg/m^2	IV infusion	1000ml 0.9% NaCl over 4 hours
4, 5,9,10	1	[d]Methotrexate	12000mg/m^2	IV infusion	1000ml 0.9% NaCl over 4 hours
4, 5, 9,10	2	Folinic Acid	15mg/m^2 every 6 hours	IV infusion	100ml 0.9% NaCl over 10minutes. Begin 24 hours after starting high dose methotrexate and continue until 6 hours after the methotrexate concentration has fallen below 0.15micromol/L
Surgery (Week 11)					
Postoperative MAP (Weeks 12 through 29)					
12, 17, 22,26	1,2	[a]DOXOrubicin	37.5mg/m^2	[b]IV push	N/A
12, 17	1, 2	[c]CISplatin	60mg/m^2	IV infusion	1000ml 0.9% NaCl over 4 hours
15, 16, 20, 21, 24, 25, 28, 29	1	[d]Methotrexate	12000mg/m^2	IV infusion	1000ml 0.9% NaCl over 4 hours
15, 16, 20, 21, 24, 25, 28, 29	2	Folinic Acid	15mg/m^2 every 6 hours	IV infusion	100ml 0.9% NaCl over 10minutes. Begin 24 hours after starting high dose methotrexate and continue until 6 hours after the methotrexate concentration has fallen below 0.15micromol/L or 11 doses have been given to T=84hr

[a]Lifetime cumulative dose of DOXOrubicin is 450mg/m^2

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below[i] and to the age of the patient.

[b]Alternatively DOXOrubicin may be administered as a continuous infusion over 48 hours via a central line (EURAMOS-1 trial).

[c]**Pre and post hydration therapy required for CISplatin**

See local hospital policy recommendations.

Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate ($MgSO_4$) (+/-KCl 10-20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above

Post hydration: Administer 1000 ml 0.9% NaCl over 60mins

1. Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload (3,4).

[d]**Methotrexate :**
Hydration and Alkalinisation regimens are required with methotrexate. See below for **suggested or** Refer to local policy

GFR to be calculated prior to administration of methotrexate infusion
Adequate hydration and urine output are essential for the rapid clearance of methotrexate.

- Commence pre-hydration with sodium bicarbonate containing infusions at125mls/m^2/hr at least 6 hours prior to methotrexate infusion.
- **Hydration** with at least 3L/m^2/24 hours of **IV fluids** throughout treatment is essential until the methotrexate level is <0.15x 10^{-8} M (0.15micromol/L)
- Urine pH should be ≥ 7.0 prior to commencement and during the methotrexate and folinic acid rescue. Check urine pH at regular intervals (6 hourly)
- **Alkalinisation** can be achieved with 50mmol of sodium bicarbonate over 8 hours in 1000ml sodium chloride 0.9%.
  (This volume administered for alkalinisation is included in the total volume of hydration.)
  - Check urine pH at regular intervals (6 hourly)
  - If the target pH is not reached adjust the sodium bicarbonate concentration to maintain the urinary pH ≥ 7.0
- **Potassium** should be supplemented according to the local policy.
- Check **fluid balance** at regular intervals (4 hourly) through each day. (Furosemide may be administered if fluid output falls below 400mls/m^2in a 4 hour period).
- **Methotrexate levels** must be taken 24, 48 hours, 72 hours, 96 hours and 120 hours as appropriate after commencement of the initial methotrexate infusion.

Continue alkalinisation, hydration and folinic acid rescue (Table 1) until methotrexate level is <0.15x 10^{-8} M (0.15micromol/L)

- Severe toxicity is anticipated if there is > 100% rise in serum creatinine level within 24hours after the start of the methotrexate infusion and/or the serum methotrexate levels are within the "toxicity range" on the methotrexate excretion curve (see Table 2below for upper limits of serum methotrexate levels). **If this is suspected:**
  - Continue hydration and alkalinisation of urine as described above
  - Increase the dose of folinic acid (see Table 2below)*
  - Consider the use of carboxypeptidase

Table2: Table for the Calculation of Folinic Acid Rescue on the basis of Methotrexate Levels

Time after starting Methotrexate infusion	Methotrexate Plasma Concentration micromol/L					
	<0.2	**0.2-0.7**	**0.71-2**	**2.1-19.9**	**20-100**	**>100**
24 hours	No folinic Acid	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	60mg/m^2 every 6 hours	Inform Consultant
48 hours	No folinic Acid	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	150mg/m^2 every 6 hours	300mg/m^2 every 3 hours	Inform Consultant
72 hours	No folinic Acid	30mg/m^2 every 6 hours	150mg/m^2 every 6 hours	750mg/m^2 every 3 hours	3000mg/m^2 every 3 hours	Inform Consultant

*Consideration may also be given to using alternative folinic acid dosing as recommended by eviQ (2)

If the methotrexate level is >100 the appropriate dose of folinic acid can be calculated using the formula below (Table 3).

Table 3: Guidance for the adjustment of folinic acid during delayed methotrexate excretion

Guidance for the adjustment of folinic acid during delayed methotrexate excretion

Upper limit of serum methotrexate:

At 24 hours is 20micromol/L

At 48 hours is 2micromol/L

At 72 hours is 0.2micromol/L

Total daily dose of folinic acid* = Patient's actual serum methotrexate x standard daily dose of folinic acid

Upper limit of serum methotrexate for the actual day and time

*Higher doses of folinic acid should be given IV every 3 hours

It is possible to reduce the dose of folinic acid at 48 and 72 hours in relation to the reduction in the methotrexate level. However if folinic acid is to continue at 96 hours then any previous increase in dose should be maintained.

Note: Always continue to monitor urine pH and give more sodium bicarbonate if pH <7 to prevent precipitation of methotrexate in acidic urine and consequent renal damage.

ELIGIBILTY:

- Indications as above
- Age≤ 40 years
- ECOG status 0-2
- ANC 1.5x10^9/L, platelets 100x10^9/L
- GFR > 70mls/min/1.73m^2

EXCLUSIONS:

- Hypersensitivity to methotrexate, DOXOrubicin, CISplatin any of the excipients
- Congestive heart failure (LVEF < 50%) or other significant heart disease
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Coagulation profile
- Urinalysis (dip stick) for blood, protein and glucose
- ECG
- MUGA or ECHO (LVEF > 50% to administer DOXOrubicin) if >65 years or if clinically indicated.
- Audiology and creatinine clearance if clinically indicated

Regular tests:

- FBC, renal and liver profile prior to each treatment and as indicated.
- Daily creatinine while on methotrexate
- If clinically indicated MUGA scan or echocardiogram
- Audiology as clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

Haematological:

Table 4: Dose modification of DOXOrubicin and CISplatin for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose Modification of DOXOrubicin and CISplatin
<0.75	or	<75	Delay and repeat within 3-4 days until criteria are met Retreat at full dose unless previous dose reduction. For repeated delay (> 7 days) use G-CSF. If delayed > 7 days in spite of G-CSF reduce CISplatin by25%.
Febrile neutropenia	All Grade 4 Consider for grade 3		Add G-CSF. Further episodes despite G-CSF: reduce CISplatin by 25%.

Table 5: Dose modification of Methotrexate for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose Modification of Methotrexate
<0.25	or	<50	Delay until recovery

Renal and Hepatic Impairment: See table 6 below and eligibility criteria for treatment.

Non-haematological toxicity:

Table 6: Dose modification schedule for DOXOrubicin, CISplatin and Methotrexate based on adverse events

Drug	Adverse reaction	Recommended dose modification	
DOXOrubicin	Mucositis : Grade 4 mucositis or Repeated Grade 3	Delay until resolved and reduce subsequent doses of DOXOrubicin to 60mg/m^2per course.	
	Hepatic Toxicity	Reduce DOXOrubicin as follows: **Bilirubin Concentration (micromole/L)**	**% Dose**
		0 – 21(0 -1.24 mg/dL)	100%
		22 – 35 (1.25-2.09 mg/dL)	75%
		36 – 52 (2.1 -3.05 mg/dL)	50%
		53 – 86(3.06-5.0 mg/dL)	25%

Drug	Adverse reaction	Recommended dose modification	
		> 87 (> 5.0 mg/dL)	0%
	Cardiotoxicity LVEF < 50% Or SF < 28%	Repeat ECHO or MUGA in one week. If within normal range proceed with chemotherapy. If LVEF does not normalize, omit all further DOXOrubicin	
CISplatin	Peripheral Neuropathy Grade1 Grade ≥ 2 Peripheral neuropathy	Reduce CISplatin by 25% for all future courses. Omit CISplatin for all further doses	
	Renal toxicity Serum creatinine> 1.5 x baseline or GFR<70mL/min/1.73 m^2	Delay for one week. If renal function does not improve, omit CISplatin and give DOXOrubicin alone. Resume CISplatin at future courses if GFR≥70mL/min/1.73 m^2.	
	Hearing ≥ Grade 2	Discontinue CISplatin if hearing loss extends to 2kHz or lower frequencies.	
Methotrexate	Grade 3-4 Mucositis or diarrhea after MTX If persists for >1 Week and is present on Day29 of MAP cycle	Consider folinic acid rescue adjustment. Omit Day 29 methotrexate (of this cycle only) and proceed to next cycle (or surgery).	
	Renal toxicity GFR <70mL/min/1.73m^2	Delay until recovery. If renal function does not improve within 1 week, omit methotrexate and proceed to next possible cycle. If renal function subsequently improves, methotrexate can be resumed.	
	Abnormal LFTs Not methotrexate induced : LFTs elevated Probably methotrexate induced i.e. up to 3weeks after methotrexate Bilirubin > 1.25 xULN	Delay one week. Give if ALT < 10 x ULN. It is expected that patients receiving high dose Methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to two weeks following the methotrexate infusion and will not be considered toxicity requiring discontinuation of the drug. Persistent hyperbilirubinemia for longer than three weeks should result in discontinuation of MTX.	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Methotrexate:	Moderate	**(Refer to local policy)**
DOXOrubicin:	Moderate	**(Refer to local policy)**
CISplatin:	High	**(Refer to local policy)**

PREMEDICATIONS: Hydration prior and post CISplatin administration (Refer to local policy or see recommendations above).

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately. **Consider use of G-CSF on further cycles as Table 4.**

DOXOrubicin

- **Extravasation:** DOXOrubicin may cause pain and tissue necrosis if extravasated. **(Refer to local extravasation guidelines).**
- **Cardiac Toxicity:** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.

CISplatin

- **Renal toxicity:** Renal toxicity is common with CISplatin. Encourage oral hydration.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle**.**

Methotrexate

- **High dose methotrexate**: Monitoring of methotrexate levels is essential as delayed methotrexate excretion is potentially an emergency situation. Renal function must be evaluated prior to treatment and patients with creatinine clearance less than 70mL/min/1.73m^2 should not receive high dose methotrexate. Methotrexate exits slowly from third space compartments (e.g. pleural effusions or ascites), resulting in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

DRUG INTERACTIONS:

- Concurrent administration of calcium channel blockers with DOXOrubicin should be avoided as they may decrease the clearance of DOXOrubicin.
- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors and penicillins reduces renal clearance of methotrexate and these drugs should be avoided when using high dose methotrexate. Cotrimoxazole and ciprofloxacin also interact.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. EURAMOS-1 Clinical Trial Protocol V4 February 2015. Available at http://www.euramos.org/media/1258/euramos1_protocol.pdf
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Version	Date	Amendment	Approved By
1	22/02/2018		Prof Maccon Keane
2	01/05/2019	Treatment table amended to include alternative administration of DOXOrubicin (continuous IV infusion).	Prof Maccon Keane
3	22/04/2020	Reviewed. Update of emetogenic potential	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[ii]Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:

• high cumulative dose, previous therapy with other anthracyclines or anthracenediones

• prior or concomitant radiotherapy to the mediastinal/pericardial area

• pre-existing heart disease

• concomitant use of other potentially cardiotoxic drugs

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient