Chemotherapy Protocol

Sarcoma

DOXORUBICIN-METHOTREXATE (cycles 5-6)

Inpatient Regimen

There are multiple versions of this protocol in use. Please ensure you have the correct version and prescribe the correct number of cycles.

Regimen

- Sarcoma – InP-Doxorubicin-Methotrexate (cycles 5-6)

Indication

- Operable osteosarcoma

Toxicity

Drug	Adverse Effect
Cisplatin	Neuropathy, neurotoxicity, ototoxicity
Doxorubicin	Cardiomyopathy, alopecia, urinary discolouration (red)
Methotrexate	Stomatitis, conjunctivitis, renal toxicity

The presence of a third fluid compartment e.g. ascites, pleural effusion or other oedema may delay the clearance of methotrexate and increase toxicity and should be resolved before methotrexate administration.

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

Monitoring

- FBC, LFTs and U&Es (including uric acid and phosphate) prior to day one of treatment
- Ensure adequate cardiac function before starting therapy. Baseline LVEF should be measured in patients with a history of cardiac problems, cardiac risk factors or in the elderly. Discontinue doxorubicin if cardiac failure develops

Methotrexate

- FBC, LFTs and U&Es prior to day one of treatment
- GFR measurement either by EDTA or 24 hour urine collection prior to methotrexate infusion. The creatinine clearance must be 50ml/min or more for the methotrexate in this regimen to be administered
- Methotrexate levels taken every 24 hours starting 24 hours after the end of the infusion until the level is below 0.1micromol/L

- Urinary pH every two hours as a minimum until the methotrexate level is below 0.1micromol/L

- Strict fluid balance chart to be maintained throughout methotrexate administration with appropriate action taken if positive by more than 2kg/L.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

In this protocol drug dosages should be modified as little as possible. If necessary, delay treatment in order to administer full doses. Decisions regarding the possibility of proceeding with chemotherapy after a delay should be re-evaluated at least every 3-4 days.

Haematological

Consider blood transfusion or erythropoietin if the patient is symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Doxorubicin

Criteria	**Eligible Level**
Neutrophil	equal to or more than $0.75x10^9$/L
Platelets	equal to or more than $75x10^9$/L

On day one of the cycle containing doxorubicin if the neutrophils are less than $0.75x10^9$/L and / or the platelet count is less than $75x10^9$/L delay treatment for 3-4 days until these criteria are met. Treatment may continue at full dose unless there has been a previous dose reduction. For a repeated delay of more than seven days use growth factors rather than dose reduce.

For a NCI-CTC grade 4 (and possible grade 3) febrile neutropenia prescribe growth factors with the next cycle.

Methotrexate

Methotrexate should only be delayed (no dose reductions apply) until recovery if the neutrophil count is less than $0.25x10^9$/L or the platelets are less than $50x10^9$/L.

Hepatic Impairment

There is a higher risk of toxicity in patients with concomitantly impaired renal function, consider dose reduction.

Drug	Bilirubin µmol/L		AST/ALT units	Dose (% of original dose)
Doxorubicin	less than 30	and	2-3xULN	75%
	30-50	and/or	more than 3xULN	50%
	51-85		N/A	25%
	more than 85		N/A	omit
Methotrexate	less than 50	and	less than 180	100%
	51-85	or	more than 180	75%
	more than 85		N/A	omit

Transient increases in bilirubin and transaminases, lasting up to two weeks, are likely following methotrexate infusion and should not be considered an indication to stop treatment. Persistent hyperbilirubinaemia (bilirubin above 1.25xULN) and/or grade 3/4 hypertransaminasemia lasting longer than three weeks should result in discontinuation of the drug.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Doxorubicin	less than 10	Consider dose reduction in severe renal failure
Methotrexate	50 or greater	100%

A creatinine clearance of 50ml/min or more is required to proceed with the methotrexate element of this regimen. Consider the appropriateness of regimen if dose reductions due to impaired renal function are required for other agents.

Other

Doxorubicin

If the LVEF is less than 50% or the SF less than 28% repeat the ECHO or MUGA in seven days. If this is within normal limits continue with chemotherapy. If the LVEF does not normalise omit all further doxorubicin.

Regimen

28 day cycle for 2 cycles, following on from four cycles of the cisplatin containing regimen

Body surface area should be calculated from a standard nomogram. Do not attempt to correct for amputation. Patients should be re-weighed after surgery and the body surface area re-calculated.

Drug	Dose	Days	Administration
Doxorubicin	37.5mg/m^2	1,2	Intravenous infusion in 48ml sodium chloride 0.9% over 24 hours
Methotrexate	12000mg/m^2	15, 22	Intravenous infusion in 1000ml sodium chloride 0.9% over 4 hours

Dose Information

- Doxorubicin will be dose banded according to the agreed bands
- The maximum lifetime cumulative dose of doxorubicin is 450mg/m². However prior radiotherapy to the mediastinal / pericardial area should receive a lifetime cumulative doxorubicin dose of no more than 400mg/m².
- Methotrexate (intravenous) will be dose banded according to the agreed bands

Administration Information

Extravasation

- Doxorubicin – vesicant
- Methotrexate – inflammitant

Other

- A central line must be in place to administer the doxorubicin
- The methotrexate infusion must not be started until the urinary pH is above 7. This urinary pH must be maintained throughout the methotrexate infusion and until the methotrexate level is 0.1micromol/L or below

Additional Therapy

This is an inpatient regimen please ensure all supportive and take home medicines are prescribed on the inpatient chart or general electronic prescribing system.

Doxorubicin

- Antiemetics

  Starting 15-30 minutes prior to chemotherapy

  - dexamethasone 4mg twice a day for 3 days oral or intravenous
  - metoclopramide 10mg three times a day for 3 days and then 10mg when required oral or intravenous

Methotrexate

- Hydration

  The following fluid regimen is recommended as hydration. Fluid hydration should start at least six hours prior to methotrexate. This schedule should be repeated every 12 hours until the methotrexate level is below 0.1 micromol/L

  - Furosemide 40mg once only dose when required for the treatment of fluid overload or to maintain urine output oral or intravenous bolus

  - Sodium chloride 0.9% with 20mmol potassium chloride 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7

  - Glucose 5% with potassium chloride 27mmol 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7

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  - Glucose 5% with potassium chloride 27mmol 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7

- Antiemetics

  Starting 15-30 minutes prior to intravenous methotrexate

  - dexamethasone 4mg twice a day for 3 days oral or intravenous
  - metoclopramide 10mg oral three times a day for three days then 10mg three times a day when required
  - ondansetron 8mg twice a day for 3 days oral or intravenous

- Post-treatment with intravenous methotrexate

  - folinic acid 30mg every 3 hours intravenous bolus beginning 24 hours after the start of the methotrexate infusion and continued until the methotrexate levels are below 0.1micromol/L. This may be given orally from dose 5 onwards if the patient is able to tolerate oral therapy. If levels of methotrexate are above 2micromol/L additional folinic acid may be necessary. See advice from a senior member of staff.

- Mouthcare for the prophylaxis or treatment of mucositis in accordance with local guidelines

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- A significant number of drugs interact with intravenous methotrexate. At the doses used in this protocol this can lead to significant toxicity or reduction in efficacy. Always check for drug interactions before prescribing any additional medication.

Coding

- Procurement – X71.5
- Delivery – not required

References
1. Ferrari S, Ruggieri P, Cefalo G et al. Neoadjuvant chemotherapy with methotrexate, cisplatin and doxorubicin with or without ifosfamide in non-metastatic osteosarcoma of the extremity. An Italian sarcoma group trial ISG/OS-1. J Clin Oncol 2012; 30 (17): 2112-2118.
2. Ferrari S, Meazza C, Palmerini E et al. Non-metastatic osteosarcoma of the extremity. Neoadjuvant chemotherapy with methotrexate, cisplatin, doxorubicin and ifosfamide. An Italian Sarcoma Group Study (ISG/OS-OSS). Tumori 2014; 100 (6): 612-619.

REGIMEN SUMMARY

InP-Doxorubicin-Methotrexate (cycles 5-6)

Other than those listed below, supportive medication for this regimen will not appear in Aria as prescribed agents. The administration instructions for each warning describes the agents which must be prescribed on the in-patient chart or general electronic prescribing system

Day 1, 2 (Doxorubicin)

1. Warning – Check supportive medicines
   Administration Instructions
   1. Dexamethasone 4mg twice a day, days 1 to 3 oral or intravenous
   2. Metoclopramide 10mg three times a day, days 1 to 3 then 10mg three times a day when required oral or intravenous
   3. Consider gastric protection
   4. Consider mouthwashes

2. Doxorubicin 37.5mg/m^2 intravenous infusion in 48ml sodium chloride 0.9% over 24 hours

Day 15, 22 (Methotrexate)

1. Warning – Check supportive medication prescribed
   Administration Instructions
   1. Furosemide 40mg oral or intravenous
   2. Fluids repeated on a 12 hourly cycle to maintain fluid balance, urine output and pH above 7 until methotrexate level is below 0.1micromol/L
      - sodium chloride 0.9% with potassium chloride 20mmol 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7
      - glucose 5% with potassium chloride 27mmol1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary ph above 7
      - sodium chloride 0.9% with potassium chloride 20mmol 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7
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      - glucose 5% with potassium chloride 27mmol 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary ph above 7
   3. Dexamethasone 4mg twice a day for 3 days oral or intravenous
   4. Metoclopramide 10mg three times a day for 3 days and then 10mg three times a day when required oral or intravenous
   5. Ondansetron 8mg twice a day for 3 days oral or intravenous
   6. Folinic acid 30mg every 3 hours intravenous beginning 24 hours after the start of the methotrexate infusion and continued until the methotrexate levels are below 0.1micromol/L. This may be given orally from dose 5 onwards
   7. Consider gastric protection
   8. Consider mouthwashes

2. Methotrexate 12000mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over four hours

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Sept 2015	None	Dr Deborah Wright Pharmacist	Dr Nicola Keay Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.