Chemotherapy Protocol

LYMPHOMA

CYTARABINE-METHOTREXATE

Inpatient Regimen

Regimen

- Lymphoma – InP-Cytarabine-Methotrexate

Indication

- Non-Hodgkin's Lymphoma (CNS disease)

Toxicity

Drug	Adverse Effect
Cytarabine	CNS toxicity, conjunctivitis, flu-like syndrome, pulmonary toxicity, gastro-intestinal toxicity
Methotrexate	Stomatitis, mucositis, 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 hence 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

Drugs

- FBC, LFTs and U&Es prior to day one of treatment
- GFR measurement either by EDTA or a 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 48 hours after the start 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 2 kg/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.

Haematological

There are no dose modifications for haematological toxicity. Treatment should be delayed until the minimum criteria, described in the table below, are reached.

Criteria	**Eligible Level**
Neutrophil	equal to or more than $1x10^9$/L
Platelets	equal to or more than $100x10^9$/L

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

Hepatic Impairment

Please note that the approach may be different if abnormal liver function tests are due to disease involvement.

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

Drug	**Bilirubin (µmol/L)**		**AST/ALT units/L**	**Dose (% of original dose)**
Cytarabine	more than 34			50% Escalate doses on subsequent cycles in the absence of toxicity
Methotrexate	less than 50	and	less than180	100%
	51-85	or	more than 180	75%
	more than 85		N/A	omit

Transient increases in bilirubin and transaminases lasting up to 2 weeks are likely following methotrexate infusion and should not be considered and indication to stop treatment. Persistent hyperbilirubinaemia and/or NCI-CTC grade 3-4 hypertransaminasemia for longer than 3 weeks should result in discontinuation of the drug.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cytarabine	*50 or greater	100%
Methotrexate	*50 or greater	100%

* Limits reflect local practice and may vary from published sources

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Where appropriate, if dose reductions made at cycle one are well tolerated, dose increases can be considered on subsequent cycles according to tolerability.

Cytarabine

Cytarabine may cause conjunctivitis. The prophylactic use of corticosteroid eye drops may reduce the incidence of this ocular toxicity

Regimen

21 day cycle for up to 4 cycles

Drug	Dose	Days	Administration
Methotrexate	500mg/m^2	1	Intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes
Methotrexate	3000mg/m^2	1	Intravenous infusion in 1000ml sodium chloride 0.9% over 180 minutes
Cytarabine	2000mg/m^2 every 12 hours	2 and 3 (4 doses)	Intravenous infusion in 100ml sodium chloride 0.9% over 60 minutes

New cycles begin on the day that the neutrophil count recovers to 1x10^9/L or more and the unsupported platelet count is 100x10^9/L or greater

Dose Information

- Cytarabine will be dose banded according to the agreed bands
- Methotrexate will be dose banded according to the agreed bands

Administration Information

Extravasation

- Cytarabine - neutral
- Methotrexate - inflammitant

Other

- 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.

- 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
  - 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
  - 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 27mmol potassium chloride 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 chemotherapy

  - dexamethasone 4mg twice a day for 5 days oral or intravenous
  - metoclopramide 10mg three times a day when required oral or intravenous
  - ondansetron 8mg twice a day for 5 days oral or intravenous

- Post-treatment with intravenous methotrexate

    - 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 if the patient is able to tolerate oral therapy. If levels of methotrexate are above 2micromol/L additional folinic acid may be necessary. Seek advice from a senior member of staff.

- Corticosteroid eye drops such as prednisolone 0.5% or dexamethasone 0.1% one drop into both eyes four times a day for 4 days starting on day 2.

- Growth factor to be continued until the neutrophil count is above $1x10^9$/L. For example:

    - filgrastim or bioequivalent 30 million units once a day from day 6 subcutaneous
    - lenograstim or bioequivalent 33.6 million units once a day from day 6 subcutaneous
    - pegfilgrastim or bioequivalent 6mg once only day 4 subcutaneous

- Mouthwashes according to local or national policy on the treatment of mucositis

- 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.

- In female patients consider norethisterone 5mg three times a day oral to delay menstruation

- Anti-infective prophylaxis as follows:
    - aciclovir 400mg twice a day oral
    - pentamidine 300mg nebule once a month
    - fluconazole 50mg once a day

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.

Coding

- Procurement – X71.2

- Delivery – Not Required

References
1.Ferreri AJ, Reni M, Foppoli M et al. International Extranodal Lymphoma Study Group (IELSG). High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. Lancet. 2009;374 (9700):1512-20.

REGIMEN SUMMARY

InP-Cytarabine-Methotrexate

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

1. Warning – Check supportive medication prescribed

   Administration Instructions
   1. Dexamethasone 4mg twice a day, days 1 to 5 oral or intravenous
   2. Metoclopramide 10mg three times a day when required oral or intravenous
   3. Ondansetron 8mg twice a day, days 1 to 5 oral or intravenous
   4. Furosemide 40mg when required oral or intravenous
   5. 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
      - 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% 1000ml with potassium chloride 27mmol intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary ph above 7
   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. Prednisolone 0.5% or dexamethasone 0.1% eye drops one drop into both eyes four times a day, days 2 to 5
   8. Aciclovir 400mg twice a day oral
   9. Fluconazole 50mg once a day oral
   10. Pentamidine nebule 300mg once a month
   11. Growth factors continued until the neutrophil count is above $1x10^9$/L
      - Filgrastim or bioequivalent 30 million units once a day from day 6 subcutaneous
      - Lenograstim or bioequivalent 33.6 million units once a day from day 6 subcutaneous
      - Pegfilgrastim or bioequivalent 6mg once only on day 4 subcutaneous
   12. Consider gastric protection
   13. Consider mouthwashes
   14. Consider norethisterone 5mg three times a day in menstruating women

2. Methotrexate 500mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes

   Administration Instructions
   Monitor fluid balance, urine output, weight and urinary pH

3. Methotrexate 3000mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 180 minutes

   Administration Instructions
   Monitor fluid balance, urine output, weight and urinary pH

Days 2 and 3

4. Warning – Check supportive medication prescribed

   Administration Instructions
   1. Dexamethasone 4mg twice a day, days 1 to 5 oral or intravenous
   2. Metoclopramide 10mg three times a day when required oral or intravenous
   3. Ondansetron 8mg twice a day, days 1 to 5 oral or intravenous
   4. Furosemide 40mg when required oral or intravenous
   5. 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
      - 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% 1000ml with potassium chloride 27mmol intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary ph above 7
   6. 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

7. Prednisolone 0.5% or dexamethasone 0.1% eye drops one drop into both eyes four times a day, days 2 to 5
8. Aciclovir 400mg twice a day oral
9. Fluconazole 50mg once a day oral
10. Pentamidine nebule 300mg once a month
11. Growth factors continued until the neutrophil count is above $1x10^9/L$
    - Filgrastim or bioequivalent 30 million units once a day from day 6 subcutaneous
    - Lenograstim or bioequivalent 33.6 million units once a day from day 6 subcutaneous
    - Pegfilgrastim or bioequivalent 6mg once only on day 4 subcutaneous
12. Consider gastric protection
13. Consider mouthwashes
14. Consider norethisterone 5mg three times a day in menstruating women

4. Cytarabine 2000mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 60 minutes twice a day

Administration Instructions

Cytarabine doses are to be given at 12 hour intervals

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Feb 2018	Cytarabine infusion volume changed to 100ml	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	Aug 2016	Header changed Toxicities removed Start time for methotrexate levels changed from 24 hours to 48 hours after the start of the infusion Renal impairment guidance updated Metoclopramide dose and duration updated "Bolus" removed from "intravenous bolus" for supportive medication throughout text Growth factor units updated Mucositis recommendation changed OPCS code updated 27mmol potassium chloride added to glucose hydration fluid CSCCN bands removed Platelets levels changed to $100x10^9$/L from $90x10^9$/L Disclaimer added	Donna Kimber Pharmacy Technician Rebecca Wills Pharmacist	Dr Deborah Wright Pharmacist
1	August 2012	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Alison Milne Consultant Haematologist Dr Andrew Davies 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 Hospital 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 that occur as a result of following these guidelines.