

Chemotherapy Protocol

LYMPHOMA

METHOTREXATE

Inpatient Regimen

Regimen

- Lymphoma – InP-Methotrexate

Indication

- Non-Hodgkin's Lymphoma (NHL), in particular treatment of primary and secondary CNS lymphoma or as CNS prophylaxis following primary treatment for high grade NHLs.

Toxicity

Drug	Adverse Effect
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

Drugs

- 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 beginning 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 2kg/L.
- Ensure the patient has no ascites, pleural effusion or oedema prior to administration of high dose methotrexate.

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 minimum criteria, described in the table below, are reached.

Criteria	Eligible Level
Neutrophil	equal to or more than $1 \times 10^9/L$
Platelets	equal to or more than $100 \times 10^9/L$

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L)

Hepatic Impairment

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

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

Drug	Bilirubin ($\mu\text{mol/L}$)		AST/ALT units/L	Dose (% of original dose)
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 2 weeks are likely following methotrexate infusion and should not be considered an 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)
Methotrexate	*50 or greater	100%

* Limits reflect local practice and may vary from published sources

Methotrexate can cause severe renal impairment that can then lead to raised levels and further toxicity. Renal function must be monitored daily until levels are below 0.1micromol/L. It is imperative that urinary pH is maintained above pH 7, through the administration of sodium bicarbonate, before starting and during the administration of methotrexate, and continued until methotrexate levels are less than 0.1micromol/L.

Monitor fluid balance carefully and give intravenous furosemide if fluid overload occurs or urine output falls to less than 400ml/m² in any 4-hour period.

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 at 72 hours additional folinic acid may be necessary. Always seek advice from a senior member of staff (consultant should always be informed of raised methotrexate levels or if a rapid deterioration in renal function occurs).

Glucarpidase can be considered for methotrexate toxicity. The decision to prescribe glucarpidase must only be made by a consultant and in accordance with the NHSE commissioning policy on glucarpidase.

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.

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.

In addition to the renal and hepatic dysfunction described above methotrexate can also cause significant mucositis. Ensure the patient has adequate mouthwashes and good oral hygiene practices.

Regimen

1 cycle will be set in Aria

Drug	Dose	Days	Administration
Methotrexate	3000 - 6000mg/m ²	1	Intravenous infusion in 1000ml sodium chloride 0.9% over 240 minutes

The next cycle begins on the day that the unsupported neutrophil count is more than 1x10⁹/L and the unsupported platelet count is more than 100x10⁹/L.

Dose Information

- Methotrexate will be dose banded in accordance with the national dose bands (100NS)
- The default dose of methotrexate will be set as 3000mg/m² in Aria

Administration Information

Extravasation

- Methotrexate – inflamitant

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 medication are prescribed on the inpatient chart or general electronic prescribing system.

- 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 when required oral or intravenous
- ondansetron 8mg twice a day for 3 days 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
- 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 or without 20-27mmol potassium chloride) 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7

- 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 at 72 hours additional folinic acid may be necessary. Seek advice from a senior member of staff.
- Mouthwashes according to local or national policy on the treatment of mucositis
- Gastric protection with a proton pump inhibitor or a H₂ 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:
 - pentamidine nebule once month

[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 – X70.3,
- Delivery – Not Required

[References](#)

1. Ferreri AJ, Reni M, Foppoli M et al. 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): 1512-1520.

REGIMEN SUMMARY

InP-Methotrexate

Inpatient Regimen

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 3 oral or intravenous
2. Metoclopramide 10mg three times a day when required oral or intravenous
3. Ondansetron 8mg twice a day, days 1 to 3 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 or without potassium chloride 20-27mmol) 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. Methotrexate levels taken every 24 hours starting 48 hours after the start of the infusion until the level is below 0.1micromol/L.
7. Pentamidine nebule 300mg once a month
8. Consider gastric protection
9. Consider mouthwashes
10. Consider norethisterone 5mg three times a day in menstruating women

2. Warning – Check methotrexate dose

Administration Instructions

The dose of methotrexate may vary. Please check the dose required with the consultant.

3. Methotrexate 3000mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 240 minutes

Administration Instructions

The dose of methotrexate may vary. Please check the dose is correct. Monitor fluid balance, urine output, weight and urinary pH. Methotrexate levels taken every 24 hours starting 48 hours after the start of the infusion until the level is below 0.1micromol/L.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	August 2018	Check for additional fluid compartment added Renal toxicity added Levels to be taken 48 hours after the start of the infusion Dose bands changed to national dose bands Potassium changed to being optional in the glucose 5% methotrexate hydration Warning added to check dose Level information added toadministration instructions Disclaimer updated	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	April 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 27mmol potassium chloride added to glucose hydration fluid Mucositis recommendation changed 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. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.