Chemotherapy Protocol

LYMPHOMA

MATRix – CYTARABINE-METHOTREXATE-RITUXIMAB-THIOTEPA

Inpatient Regimen

Regimen

- Lymphoma – InP-MATRix – Cytarabine-Methotrexate-Rituximab-Thiotepa

Indication

- Non-Hodgkin's Lymphoma (CNS disease)

Toxicity

Drug	Adverse Effect
Methotrexate	Stomatitis, mucositis, conjunctivitis, renal toxicity
Cytarabine	CNS toxicity, conjunctivitis, flu-like syndrome, pulmonary toxicity, gastro-intestinal toxicity
Rituximab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy
Thiotepa	Myelosuppression, nausea and vomiting, infertility

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. Renal function should be measured daily during methotrexate administration until methotrexate levels are less than 0.1micromol/L
- 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

- Ensure the patient has no ascites, pleural effusion or oedema prior to administration of high dose methotrexate.
- Strict fluid balance chart to be maintained throughout methotrexate administration with appropriate action taken if positive by more than 2 kg/L
- Consider monitoring serum immunoglobulin levels
- Check hepatitis B status before starting treatment with rituximab

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
Neutrophils	equal to or more than $1.5x10^9$/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 (80g/L).

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	less than or equal to 33		N/A	100%
	more than 34		N/A	50% Escalate doses in subsequent cycles in the absence of toxicity
Methotrexate*	less than 50	and	less than 180	100%
	51-85	or	more than 180	75%
	more than 85		N/A	omit
Rituximab	N/A		N/A	No dose adjustment required
Thiotepa	N/A		N/A	No formal recommendations. Thiotepa is metabolised by the liver - consider dose reduction

*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)
Cytarabine	**50 or greater	100%
Methotrexate	**50 or greater	100%
Rituximab	N/A	No dose adjustment required
Thiotepa	Mild / moderate renal impairment	No formal recommendations. Dose modification probably unnecessary – use with caution

** 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 0.1 micromol/L.

Monitor fluid balance carefully and give intravenous furosemide if fluid overload occurs or urine output falls to less than 400ml/m^2 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 2.0 micromol/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) and increase the dose of folinic as follows;

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 (https://www.england.nhs.uk/wp-content/uploads/2018/07/Glucarpidase-for-the-urgent-treatment-of-methotrexate-induced-renal-dysfunction.pdf).

NHS England will fund glucarpidase (unlicensed in UK) for adults receiving high-dose methotrexate chemotherapy (doses greater than 1g/m2);

- Who develop significant deterioration in renal function (greater than1.5x ULN and rising, or the presence of oliguria)

OR

- have toxic plasma methotrexate level

AND

- have been treated with all standard rescue and supportive measures

AND

- at risk of life-threatening methotrexate-induced toxicities

The recommended dose is one single intravenous injection of 50units/kg

Other

Older patients considered fit for MATRix therapy may receive dose reductions at the discretion of the supervising consultant

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

Methotrexate

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. Daily weights should be undertaken during hydration for methotrexate, and significant fluid retention should be managed with furosemide, as required (see 'additional therapy').

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.

Rituximab

Infusion related adverse reactions have been observed in 10% of patients treated with rituximab.

Rituximab administration is associated with the onset of cytokine release syndrome. This condition is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. It may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, acute renal failure, elevated lactate dehydrogenase (LDH) and can lead to acute respiratory failure and death. This effect on the lungs may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray.

Cytokine release syndrome frequently occurs within one or two hours of initiating the first infusion.

Hypersensitivity reactions, including anaphylaxis, have been reported following the intravenous administration of proteins. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes of starting the infusion. Medicinal products for the treatment of allergic reactions should be available for immediate use in the event of hypersensitivity developing during the administration of rituximab.

Use of rituximab may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological, cognitive or psychiatric symptoms that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed the rituximab must be permanently discontinued.

The presence of a viral upper respiratory tract infection at the time of treatment may increase the risk of rituximab associated hepatotoxicity. Patients should be assessed for any cold or flu-like symptoms prior to treatment.

Regimen

21 day cycle for up to 4 cycles

Drug	Dose	Days	Administration
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9% as per rituximab infusion guidelines
Methotrexate	500mg/m^2	2	Intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes
Methotrexate	3000mg/m^2	2	Intravenous infusion in 500ml sodium chloride 0.9% over 180 minutes
Cytarabine	2000mg/m^2 every 12 hrs	3, 4 (4 doses)	Intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes
Thiotepa	30mg/m^2	5	Intravenous infusion 100ml sodium chloride 0.9% over 30 minutes

Dose Information

- Cytarabine will be dose banded in accordance with the national dose bands (100mg/ml)
- Methotrexate will be dose banded in accordance with the national dose bands (100 NS)
- Rituximab dose will be rounded to the nearest 100mg (up if halfway)
- Thiotepa will be dose banded in accordance with the national dose bands (10mg/ml)

Administration Information

Extravasation

- Cytarabine - neutral
- Methotrexate – inflammitant
- Rituximab - neutral
- Thiotepa - neutral

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. The day one and six rituximab may be administered as an out-patient.

- Rituximab pre-medication (30 minutes prior to rituximab)

- chlorphenamine 10mg intravenous
- hydrocortisone 100mg intravenous (may be omitted if the patient is already taking steroids)
- paracetamol 1000mg oral

- Rituximab infusion reactions

  - hydrocortisone 100mg intravenous when required for rituximab infusion related reactions
  - salbutamol 2.5mg nebule when required for rituximab related bronchospasm
  - consider pethidine 25-50mg intravenous for rituximab related rigors that fail to respond to corticosteroids

- 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
    *the concentration of potassium chloride may vary across Trusts, please check local availability

- Antiemetics

  Starting 15-30 minutes prior to chemotherapy

  - dexamethasone 4mg twice a day for 5 days oral or intravenous starting on day 7
  - metoclopramide 10mg three times a day when required oral or intravenous
  - ondansetron 8mg twice a day for 5 days oral or intravenous starting on day 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 the medical staff (consultant must be informed of raised methotrexate levels and / or a rapid deterioration in renal function or output).

- 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 8.

- Growth factor should be started 24 hours after completion of chemotherapy, to be continued until the neutrophil count is above $1x10^9$/L. For example:

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

Stem Cell Mobilisation

- Haematopoietic stem cells may be mobilised from cycle 2 onwards in patients with demonstrated clinical and radiological response. Mobilisation with G-CSF (equivalent to filgrastim or bioequivalent 10mcg/kg/day) should start from 24 hours following the final dose of chemotherapy. Stem cell harvest can usually be attempted from day 13 following the first day of MATRix.

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. These include penicillins, aspirin, co-trimoxazole and NSAIDs. Tazocin should NOT be used during high dose methotrexate administration or rescue. Consider using meropenem or other alternative. Review indications for aspirin and NSAIDs and consider stopping during methotrexate treatment.

Coding

- Procurement – X71.2
- Delivery – Not Required

References
1. Ferreri AJ, Cwynarski K, et al. Chemotherapy with methotrexate, cytarabine, thiotepa (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. The Lancet Haematology. 2016; 3(5):e217-227.

REGIMEN SUMMARY

InP-MATRix-Cytarabine-Methotrexate-Rituximab-Thiotepa

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

Days 1

1. Chlorphenamine 10mg intravenous injection

2. Hydrocortisone 100mg intravenous injection

3. Paracetamol 1000mg oral
   Administration Instructions
   Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

4. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

5. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions

6. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Day 2

7. Warning – Check supportive medication prescribed
   Administration Instructions
   1. Dexamethasone 4mg twice a day on days 2 to 7 oral or intravenous
   2. Metoclopramide 10mg three times a day when required oral or intravenous
   3. Ondansetron 8mg twice a day on days 2 to 7 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
   7. Prednisolone 0.5% or dexamethasone 0.1% eye drops one drop into both eyes four times a day starting on day 3 to 10
   8. Aciclovir 400mg twice a day oral
   9. Fluconazole 50mg once a day oral
   10. Pentamidine nebule 300mg once a month
   11. Growth factors starting on day 6 and 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 6 subcutaneous
   12. Consider gastric protection
   13. Consider mouthwashes
   14. Consider norethisterone 5mg three times a day in menstruating women

8. 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

9. 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 3 and 4

10. Warning – Check supportive medication prescribed
    Administration Instructions
    15. Dexamethasone 4mg twice a dayon days 2 to 7 oral or intravenous
    16. Metoclopramide 10mg three times a day when required oral or intravenous
    17. Ondansetron 8mg twice a day on days 2 to 7 oral or intravenous
    18. Furosemide 40mg when required oral or intravenous
    19. 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
    20. 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
    21. Prednisolone 0.5% or dexamethasone 0.1% eye drops one drop into both eyes four times a day starting on day 3 to 10
    22. Aciclovir 400mg twice a day oral
    23. Fluconazole 50mg once a day oral
    24. Pentamidine nebule 300mg once a month
    25. Growth factors starting on day 6 and 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 6 subcutaneous
    26. Consider gastric protection
    27. Consider mouthwashes
    28. Consider norethisterone 5mg three times a day in menstruating women
    Administration Instructions

11. Warning – Cytarabine is TWICE a day (12 hour intervals)
    Administration Instructions
    Cytarabine is administered as a dose of 2000mg/m^2 twice a day at twelve hour intervals. This is four doses in total.

12. Cytarabine 2000mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes twice a day
    Administration Instructions
    Cytarabine is administered as a dose of 2000mg/m^2 twice a day at twelve hour intervals. This is four doses in total.

Day 5

13. Warning – Check supportive medication prescribed

Administration Instructions

29. Dexamethasone 4mg twice a dayon days 2 to 7 oral or intravenous
30. Metoclopramide 10mg three times a day when required oral or intravenous
31. Ondansetron 8mg twice a day on days 2 to 7 oral or intravenous
32. Furosemide 40mg when required oral or intravenous
33. 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
34. 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
35. Prednisolone 0.5% or dexamethasone 0.1% eye drops one drop into both eyes four times a day starting on day 3 to 10
36. Aciclovir 400mg twice a day oral
37. Fluconazole 50mg once a day oral
38. Pentamidine nebule 300mg once a month
39. Growth factors starting on day 6 and 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 6 subcutaneous
40. Consider gastric protection
41. Consider mouthwashes
42. Consider norethisterone 5mg three times a day in menstruating women

14. Thiotepa 30mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	July 2018	New document	Dr Deborah Wright Pharmacist	Dr Rob Lown Consultant Haematologist

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.