Chemotherapy Protocol

LYMPHOMA

CYCLOPHOSPHAMIDE-DOXORUBICIN-METHOTREXATE-RITUXIMAB-VINCRISTINE (RCODOX-M)

66 years and above

Inpatient Regimen

There are multiple versions of this protocol in use. The choice of protocol depends on the age of the patient and whether there is CNS disease present at diagnosis. Please ensure you have the correct version and prescribe the correct number of cycles.

Regimen

- Lymphoma – InP-RCODOX-M(65)-Cyclophosphamide-Doxorubicin-Methotrexate-Rituximab-Vincristine

Indication

- Non Hodgkin's Lymphoma including Burkitt's lymphoma either as a single regimen or alternating with R-IVAC

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrragic cystitis (rare), taste disturbances
Doxorubicin	Cardiomyopathy, alopecia, urinary discolouration (red)
Methotrexate	Stomatitis, conjunctivitis, renal toxicity
Rituximab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy
Vincristine	Peripheral neuropathy, constipation, jaw pain

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

R-CODOX-Cyclophosphamide-Doxorubicin-Rituximab-Vincristine

- 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
- Intensive post chemotherapy biochemical monitoring is mandatory in patients with bulky disease and should be strongly considered in all patients during days 1 to 5 of treatment. This includes daily serum electrolytes, urea, creatinine, calcium and phosphorus
- Check hepatitis B status before starting treatment with rituximab

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 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. New treatment cycles should be delayed until minimum criteria detailed below are reached (day 10 methotrexate will be given irrespective of the neutrophil or platelet count).

Criteria	Eligible Level
Neutrophil	equal to or more than $1x10^9$/L
Platelets	equal to or more than $75x10^9$/L

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

Hepatic Impairment

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

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

Drug	Bilirubin µmol/L		AST/ALT units/L	Dose (% of original dose)
Cyclophosphamide	N/A		N/A	Evidence suggests no dose reduction is necessary
Doxorubicin	less than 30*		2-3xULN	75%
	*30-51	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
Rituximab	N/A		N/A	No dose adjustments required
Vincristine	*30-51	or	60-180	50%
	more than 51	and	normal	50%
	more than 51	and	more than 180	omit

* Limits reflect local practice and may vary from published sources

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 and/or grade 3/4 hypertransaminasemia for longer than three weeks should result in discontinuation of the drug.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cyclophosphamide	more than 20	100%
	10-20	75%
	less than 10	50%
Doxorubicin	N/A	Consider dose reduction in severe renal failure
Methotrexate	*50 or greater	100%
Rituximab	N/A	No dose adjustment needed
Vincristine	N/A	No dose adjustment needed

* Limits reflect local practice and may vary from published sources

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.

Consider mesna in patients with pre-existing bladder disorders. Give an oral dose of 40% of the cyclophosphamide dose (rounded upwards to the nearest 400mg for oral mesna) at 0, 2 and 6 hours after the administration of cyclophosphamide.

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.

Cyclophosphamide

Consider mesna in patients with pre-existing bladder disorders.

Doxorubicin

Discontinue doxorubicin if cardiac failure develops

Methotrexate

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/m^2 in any 4-hour period.

Folinic acid 30mg every 3 hours intravenous beginning 36 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.

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.

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 maybe 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 prior to treatment may increase the risk of rituximab associated hepatotoxicity. Patients should be assessed for any cold or flu like symptoms prior to treatment.

Vincristine

Reduce the vincristine dose from 2mg to 1mg if a NCI-CTC grade 2 motor or grade 3 sensory neurological toxicity occurs. For higher toxicity grades or if toxicity increases despite dose reduction stop the vincristine.

Regimen

3 cycles in low risk disease

2 cycles in high risk disease alternating with 2 cycles of R- IVAC

1 cycle will be set in Aria

The next cycle begins on the day that the unsupported neutrophil count is more than $1x10^9$/L and the unsupported platelet count is more than $75x10^9$/L.

Drug	Dose	Days	Administration
Cyclophosphamide	800mg/m^2	1	Intravenous bolus over 10 minutes
Cyclophosphamide	200mg/m^2	2,3,4,5	Intravenous bolus over 10 minutes
Doxorubicin	40mg/m^2	1	Intravenous bolus over 10 minutes
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9% as per local guidelines
Vincristine	1.5mg/m^2 (max 2mg)	1, 8	Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
Methotrexate	100mg/m^2	10	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
Methotrexate	900mg/m^2	10	Intravenous infusion in 1000ml sodium chloride 0.9% over 23 hours
Drug (intrathecal)	**Dose**	**Days**	**Administration**
Cytarabine	70mg	1, 3	Intrathecal
Methotrexate	12.5mg	15	Intrathecal

An intensified intrathecal treatment is required for patients with CNS disease at diagnosis. This is given for the first cycle of R- CODOX-M and the first cycle of R-IVAC.

For R-CODOX-M this is as follows:

Drug (intrathecal)	Dose	Days	Administration
Cytarabine	70mg	5	Intrathecal
Methotrexate	12.5mg	17	Intrathecal

Intrathecal doses that fall on a weekend should be deferred until the next working day

Dose Information

- Cyclophosphamide will be dose banded in accordance with the national bands (20PM)
- Doxorubicin will be dose banded in accordance with the national bands (2PM)
- 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 in accordance with the national bands (methotrexate HD)
- Rituximab dose will be rounded to the nearest 100mg (up if halfway)
- Vincristine will be dose banded in accordance with the national bands (1mg/ml)
- The maximum dose of vincristine is 2mg

Administration Information

Extravasation

- Cyclophosphamide – neutral
- Doxorubicin – vesicant
- Methotrexate – inflammitant
- Rituximab - neutral
- Vincristine - vesicant

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
- The methotrexate infusion must be stopped 24 hours after the start of the first infusion regardless of the dose given

- The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines

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.

Day 1 - R-CODOX – Cyclophosphamide-Doxorubicin-Rituximab-Vincristine

- Premedication

  30 minutes prior to rituximab

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous
  - 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.

- Antiemetics

  Starting 15-30 minutes prior to chemotherapy

  - dexamethasone 4mg twice a day for 7 days oral or intravenous
  - metoclopramide 10mg three times then when required oral or intravenous
  - ondansetron 8mg twice a day for 7 days oral or intravenous

Day 10 - Methotrexate (Intravenous)

- 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 oral or intravenous when required for the treatment of fluid overload or to maintain urine output

  - 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 potassium chloride 20 or 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 when required oral or intravenous
  - ondansetron 8mg twice a day for 3 days oral or intravenous

- Post-treatment with intravenous methotrexate

  - folinic acid 30mg every 3 hours intravenous beginning 36 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.

- 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 13 subcutaneous
  - lenograstim or bioequivalent 33.6 million units once a day from day 13 subcutaneous
  - pegfilgrastim or bioequivalent 6mg once only day 13 subcutaneous

- Folinic acid 15mg four times a day oral for one day starting 24 hours after the administration of the intrathecal methotrexate dose, according to local practice

- 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

- Tumour lysis prophylaxis with cycle one only including:

  - appropriate hydration
  - rasburicase for high risk patients
  - allopurinol 300mg once a day for the first cycle only

- Anti-infective prophylaxis as follows:

    - aciclovir 400mg twice a day oral
    - pentamidine 300mg nebule once a month
    - fluconazole 50mg once a day oral

Some centres avoid the use of azole antifungal agents due to the risk of peripheral neuropathy when combined with vinca alkaloids.

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.

- HSC 2008/001: Updated national guidance on the safe administration of intrathecal chemotherapy must be followed.

- The National Patient Safety Agency report NPSA/2008/RRR04 must be followed in relation to intravenous administration of vinca alkaloids.

Coding (OPCS)

- Procurement – X71.5

- Delivery – not required

References

1. NCRI Lymphoma Group. A Clinicopathological Study in Burkitt's and Burkitt-Like Non-Hodgkin's Lymphoma. LY10. Protocol Version 2.0. September 2002.
2.Mead GM, Sydes MY, Walewski J et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitts lymphoma: results of United Kingdom Lymphoma Group LY06 study. Ann Oncol 2002; 13 (8): 1264-1274.

REGIMEN SUMMARY

InP-RCODOX-M(66)-Cyclophosphamide-Doxorubicin-Methotrexate-Rituximab-Vincristine

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 7 oral or intravenous
   2. Metoclopramide 10mg three times a day when required oral or intravenous
   3. Ondansetron 8mg twice a day, days 1 to 7 oral or intravenous
   4. Aciclovir 400mg twice a day oral
   5. Pentamidine nebule 300mg once a month
   6. Fluconazole 50mg once a day oral (consider – interacts with vincristine)
   7. Tumour lysis prophylaxis including appropriate hydration (cycle one only)
   8. Consider gastric protection
   9. Consider mouthwashes
   10. Consider norethisterone 5mg three times a day in menstruating women
   11. Consider pethidine 25-50mg intravenous for rituximab related rigors that fail to respond to corticosteroids

2. Chlorphenamine 10mg intravenous

3. Hydrocortisone 100mg intravenous

4. 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

5. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% (administer according to local guidelines)

6. Doxorubicin 40mg/m^2 intravenous bolus over 10 minutes

7. Vincristine 1.5mg/m^2 (max dose 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

8. Cyclophosphamide 800mg/m^2 intravenous bolus over 10 minutes

9. Warning – Prescribe intrathecal on intrathecal chart
   Administration Instructions
   Prescribe cytarabine 70mg intrathecal. This must be prescribed on an intrathecal chart to comply with national guidance. This warning is a reminder not a prescription. National intrathecal guidance and local intrathecal policies must be followed at all times.

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

11. Salbutamol 2.5mg nebule when required for rituximab related bronchospasm

Day 2

12. Warning – Check supportive medication prescribed
    Administration Instructions
    1. Dexamethasone 4mg twice a day, days 1 to 7 oral or intravenous
    2. Metoclopramide 10mg three times a day when required oral or intravenous
    3. Ondansetron 8mg twice a day, days 1 to 7 oral or intravenous
    4. Aciclovir 400mg twice a day oral
    5. Pentamidine nebule 300mg once a month
    6. Fluconazole 50mg once a day oral (consider – interacts with vincristine)
    7. Tumour lysis prophylaxis including appropriate hydration (cycle one only)
    8. Consider gastric protection
    9. Consider mouthwashes
    10. Consider norethisterone 5mg three times a day in menstruating women
    11. Consider pethidine 25-50mg intravenous for rituximab related rigors that fail to respond to corticosteroids

13. Cyclophosphamide 200mg/m^2 intravenous bolus over 10 minutes

Day 3

14. Warning – Check supportive medication prescribed
    Administration Instructions
    1. Dexamethasone 4mg twice a day, days 1 to 7 oral or intravenous
    2. Metoclopramide 10mg three times a day when required oral or intravenous
    3. Ondansetron 8mg twice a day, days 1 to 7 oral or intravenous
    4. Aciclovir 400mg twice a day oral
    5. Pentamidine nebule 300mg once a month
    6. Fluconazole 50mg once a day oral (consider – interacts with vincristine)
    7. Tumour lysis prophylaxis including appropriate hydration (cycle one only)
    8. Consider gastric protection
    9. Consider mouthwashes
    10. Consider norethisterone 5mg three times a day in menstruating women
    11. Consider pethidine 25-50mg intravenous for rituximab related rigors that fail to respond to corticosteroids

15. Cyclophosphamide 200mg/m^2 intravenous bolus over 10 minutes

16. Warning – Prescribe intrathecal on an intrathecal chart
    Administration Instructions
    Prescribe cytarabine 70mg intrathecal. This must be prescribed on an intrathecal chart to comply with national guidance. This warning is a reminder not a prescription. National intrathecal guidance and local intrathecal policies must be followed at all times

Day 4

17. Warning – Check supportive medication prescribed
    Administration Instructions
    1. Dexamethasone 4mg twice a day, days 1 to 7 oral or intravenous
    2. Metoclopramide 10mg three times a day when required oral or intravenous
    3. Ondansetron 8mg twice a day, days 1 to 7 oral or intravenous
    4. Aciclovir 400mg twice a day oral
    5. Pentamidine nebule 300mg once a month
    6. Fluconazole 50mg once a day oral (consider – interacts with vincristine)
    7. Tumour lysis prophylaxis including appropriate hydration (cycle one only)
    8. Consider gastric protection
    9. Consider mouthwashes
    10. Consider norethisterone 5mg three times a day in menstruating women
    11. Consider pethidine 25-50mg intravenous for rituximab related rigors that fail to respond to corticosteroids

18. Cyclophosphamide 200mg/m^2 intravenous bolus over 10 minutes

Day 5

19. Warning – Check supportive medication prescribed
    Administration Instructions
    1. Dexamethasone 4mg twice a day, days 1 to 7 oral or intravenous
    2. Metoclopramide 10mg three times a day when required oral or intravenous
    3. Ondansetron 8mg twice a day, days 1 to 7 oral or intravenous
    4. Aciclovir 400mg twice a day oral
    5. Pentamidine nebule 300mg once a month
    6. Fluconazole 50mg once a day oral (consider – may interact with vincristine)
    7. Tumour lysis prophylaxis including appropriate hydration (cycle one only)
    8. Consider gastric protection
    9. Consider mouthwashes
    10. Consider norethisterone 5mg three times a day in menstruating women
    11. Consider pethidine 25-50mg intravenous for rituximab related rigors that fail to respond to corticosteroids

20. Cyclophosphamide 200mg/m^2 intravenous bolus over 10 minutes

21. Warning – CNS disease extra intrathecal cycle 1 only
    Administration Instructions
    For patients presenting with CNS disease please prescribe an additional cytarabine 70mg intrathecal on day 5 cycle one only Intrathecal chemotherapy must be prescribed on an intrathecal chart. This is a warning, not a prescription. National intrathecal guidance and local intrathecal policies must be followed at all times.

Day 8

22. Warning – Check supportive medication prescribed
    Administration Instructions
    1. Aciclovir 400mg twice a day oral
    2. Pentamidine nebule 300mg once a month
    3. Fluconazole 50mg once a day oral (consider – may interact with vincristine)
    4. Tumour lysis prophylaxis including appropriate hydration (cycle one only)
    5. Consider gastric protection
    6. Consider mouthwashes
    7. Consider norethisterone 5mg three times a day in menstruating women

23. Vincristine 1.5mg/m^2 (max dose 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

Day 10

24. Warning – Check supportive medication prescribed
    Administration Instructions
    1. Furosemide 40mg when required 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
        - 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 or 27mmol) 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 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 36 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. Growth factors started and continued until the neutrophil count is above 1x10^9/L
        - filgrastim or bioequivalent 30 million units once a day from day 13 subcutaneous
        - lenograstim or bioequivalent 33.6 million units once a day from day 13 subcutaneous
        - pegfilgrastim or bioequivalent 6mg once only on day 13 subcutaneous
    8. Aciclovir 400mg twice a day oral
    9. Pentamidine 300mg nebule once a month
    10. Fluconazole 50mg once a day oral
    11. Tumour lysis prophylaxis including appropriate hydration (cycle one only)
    12. Consider gastric protection
    13. Consider mouthwashes
    14. Consider norethisterone 5mg three times a day in menstruating women

25. Methotrexate 100mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 1 hour
    Administration Instructions
    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.

26. Methotrexate 900mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 23 hours
    Administration Instructions
    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.

Day 15

27. Warning – Prescribe intrathecal on intrathecal chart
    Administration Instructions
    Prescribe methotrexate 12.5mg intrathecal. This must be prescribed on an intrathecal chart to comply with national guidance. This warning is a reminder not a prescription. National intrathecal guidance and local intrathecal policies must be followed at all times

Day 17

28. Warning – CNS disease extra intrathecal cycle 1 only
    Administration Instructions
    For patients presenting with CNS disease please prescribe an additional methotrexate 12.5mg intrathecal at cycle 1 only. Intrathecal chemotherapy must be prescribed on an intrathecal chart. This is a warning, not a prescription. National intrathecal guidance and local policies must be followed at all times.
    Folinic acid 15mg four times a day oral for one day starting 24 hours after the administration of intrathecal methotrexate, according to local practice

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	Aug 2018	Check for additional fluid compartment added Renal toxicity added Dose bands changed to national bands Potassium changed to being optional in the glucose 5% methotrexate hydration Fluconazole interaction added Paracetamol administration instructions Methotrexate levels added to administration instructions Intrathecal changed to a warning Disclaimer updated	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	Sept 2016	Header changed Toxicities removed Hepatic and renal impairment guidance updated Antiemetics clarified Administration information for hydrocortisone pre med removed Metoclopramide dose and duration updated “Bolus” removed from “intravenous bolus” for supportive medication throughout text Start of methotrexate levels changed from 24 hours after the end of the infusion 48 hours after the start of the infusion Growth factor units updated Mucositis recommendation changed OPCS code updated 27mmol potassium chloride added to glucose hydration fluid “according to local practice” and “oral” added to folinic acid instructions following intrathecal methotrexate CSSCN agreed bands removed Regimen summary numbering updated. 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 Andrew Davies Consultant Medical Oncologist Dr Alison Milne 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.