

Chemotherapy Protocol

LYMPHOMA

CYTARABINE-ETOPOSIDE-IFOSFAMIDE-RITUXIMAB

(RIVAC)

65 years and below

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-RIVAC(65)-Cytarabine-Etoposide-Ifosfamide-Rituximab

[Indication](#)

- Non Hodgkin's Lymphoma (Burkitts lymphoma or diffuse large B cell lymphoma) that is CD20 positive alternating with RCODOX-M
- Radical or curative intent

[Toxicity](#)

Drug	Adverse Effect
Cytarabine	CNS toxicity, conjunctivitis, flu-like syndrome, pulmonary toxicity, gastro-intestinal toxicity
Etoposide	Hypotension on rapid infusion, hyperbilirubinaemia
Ifosfamide	Haemorrhagic cystitis, encephalopathy, nephrotoxicity
Rituximab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy

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

[Monitoring](#)

[Drugs](#)

- FBC, LFTs (including albumin) and U&Es prior to day one of treatment
- EDTA or calculated creatinine clearance prior to each cycle
- Urine dip test for proteinuria and haematuria every four hours the day of and the day after ifosfamide administration. The patient should be instructed to report any signs

or symptoms of cystitis.

- Fluid balance monitoring every four hours the day of and the day after ifosfamide administration. Urine output should be maintained above 100ml/hour
- Hepatitis B screen prior to 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
Neutrophil	equal to or more than $1 \times 10^9/L$
Platelets	equal to or more than $75 \times 10^9/L$

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

[Hepatic Impairment](#)

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

Drug	Bilirubin μmol/L		AST/ALT units	Dose (% of original dose)
Cytarabine	more than 34			50% Escalate doses on subsequent cycles in the absence of toxicity
Etoposide	30-51	or	60-180	Consider dose reducing to 50%
	more than 51	or	more than180	Clinical decision
Ifosfamide	more than 20	or	more than 2.5xULN	Not recommended
	or ALP more than 2.5xULN			
Rituximab	N/A		N/A	No dose adjustments required

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cytarabine	more than 60	100%
	46-60	60%
	31-45	50%
	less than 30	omit
Etoposide	more than 50	100%
	15-50	75%
	less than 15	50%
Ifosfamide	more than 60	100%
	40-59	70%
	less than 40	Clinical decision
Rituximab	N/A	N/A

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.

Cytarabine

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

Etoposide

Where significant reductions in albumin levels occur consider reducing the dose of etoposide.

Ifosfamide

In the case of a NCI-CTC grade 1 neurological toxicity, the dose of ifosfamide may be reduced for the next cycle. If a NCI-CTC grade 2 neurological toxicity appears or neurological toxicity worsens despite dose reduction, the ifosfamide should be stopped.

Risk factors for CNS toxicity include a low albumin, renal impairment, prior administration of cisplatin, poor performance status, CNS tumour, bulky pelvic disease, concomitant psychotropic drugs and younger age. Methylene blue 50mg four times a day intravenous infusion in 100ml sodium chloride 0.9% can be used to prevent or treat ifosfamide induced encephalopathy.

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.

[Regimen](#)

2 cycles in high risk disease alternating with 2 cycles of R-CODOX-M.

The order of administration is R-CODOX-M, R-IVAC, R-CODOX-M, R-IVAC. Two doses of rituximab should be given on days 21 and 42 after the end of the last R-IVAC to make 8 doses of rituximab in total.

1 cycle will be set in Aria

The next cycle begins on the day that the unsupported neutrophil count is more than $1 \times 10^9/L$ and the unsupported platelet count is more than $75 \times 10^9/L$.

Drug	Dose	Days	Administration
Cytarabine	2000mg/m ² every 12 hours	1 and 2 (4 doses)	Intravenous infusion in 1000ml sodium chloride 0.9% over 180 minutes
Etoposide	60mg/m ²	1,2,3,4,5	Intravenous infusion in 500ml sodium chloride 0.9% over 60 minutes
Mesna	300mg/m ²	1,2,3,4,5	Intravenous infusion in sodium chloride 0.9% 100ml over 15 minutes
Ifosfamide	1500mg/m ²	1,2,3,4,5	Intravenous infusion in sodium chloride 0.9% 1000ml over 60 minutes (the ifosfamide and mesna are mixed in the same bag)
Mesna	1500mg/m ²		
Mesna	900mg/m ²	1,2,3,4,5	Intravenous infusion in sodium chloride 0.9% 1000ml over 12 hours
Rituximab	375mg/m ²	1	Intravenous infusion in 500ml sodium chloride 0.9% as per local guidelines
Drug (intrathecal)	Dose	Days	Administration
Methotrexate	12.5mg	5	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-IVAC this is as follows:

Drug	Dose	Days	Administration
Cytarabine	70mg	7, 9	Intrathecal

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

[Dose Information](#)

- Cytarabine will be dose banded according to the nationally agreed bands (100mg/ml)
- Etoposide will be dose banded according to the nationally agreed bands (20mg/ml)
- Ifosfamide will be dose banded according to the nationally agreed bands (80mg/ml)
- Mesna will be dose banded according to the nationally agreed bands (100mg/ml)
- Rituximab dose will be rounded to the nearest 100mg (up if halfway)

Administration Information

Extravasation

- Cytarabine -neutral
- Etoposide – irritant
- Ifosfamide – neutral
- Mesna - neutral
- Rituximab - neutral

Other

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

- Rituximab premedication
30 minutes prior to rituximab
 - chlorphenamine 10mg intravenous bolus
 - hydrocortisone 100mg intravenous bolus (may be omitted if the patient is already taking corticosteroids)
 - paracetamol 1000mg oral
- Rituximab infusion reactions
 - hydrocortisone 100mg intravenous bolus when required for rituximab infusion related reactions
 - salbutamol 2.5mg nebule when required for rituximab related bronchospasm
 - consider pethidine 25-50mg intravenous bolus 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 bolus
 - metoclopramide 10mg three times a day for 7 days then when required oral or intravenous bolus
 - ondansetron 8mg twice a day for 7 days oral or intravenous bolus
- Growth factors continued until the neutrophil count is above $1 \times 10^9/L$. For example:

- filgrastim or bioequivalent 30 million unit once a day from day 7 subcutaneous
- lenograstim or bioequivalent 33.6 million unit once a day from day 7 subcutaneous
- pegfilgrastim or bioequivalent 6mg once only on day 7 subcutaneous
- Folinic acid 15mg four times a day for one day starting 24 hours after the administration of the intrathecal methotrexate dose
- Corticosteroid eye drops such as prednisolone 0.5% or dexamethasone 0.1% one drop into both eyes four times a day for 4 days
- Mouthcare for the prophylaxis or treatment of mucositis in accordance with CSCCN guidelines
- 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:
 - aciclovir 400mg twice a day oral
 - pentamidine 300mg nebule once a month
 - fluconazole 50mg once a day oral

[Additional Information](#)

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

[Coding](#)

- 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-RIVAC (65)-Cytarabine-Etoposide-Ifosfamide-Rituximab

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, days 1 to 7 days then as required oral or intravenous
3. Ondansetron 8mg twice a day, days 1 to 7 oral or intravenous
4. Prednisolone 0.5% or dexamethasone 0.1% eye drops one drop into both eyes four times a day, days 1 to 4
5. Growth factor continued until the neutrophil count is above $1 \times 10^9/L$
 - filgrastim or bioequivalent 30 million units once a day from day 7 subcutaneous
 - lenograstim or bioequivalent 33.6million units once a day from day 7 subcutaneous
 - pegfilgrastim or bioequivalent 6mg once only on day 7 subcutaneous
6. Folinic acid 15mg four times a day for one day starting 24 hours after the administration of intrathecal methotrexate (normally day 6)
7. Aciclovir 400mg oral twice a day
8. Pentamidine 300mg nebule once a month
9. Fluconazole 50mg once a day
10. Consider gastric protection
11. Consider mouthwashes
12. Consider norethisterone for menstruating women
13. Consider pethidine 25-50mg intravenous bolus for rituximab related rigors unresponsive to corticosteroids

2. Chlorphenamine 10mg intravenous injection

3. Hydrocortisone 100mg intravenous injection

Administration Instructions

1. Do not administer if corticosteroids have been given as part of the antiemetic or chemotherapy regimen

4. Paracetamol 1000mg oral

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

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

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

8. Warning – Cytarabine is TWICE a day

Administration Instructions

The cytarabine is to be given twice a day at twelve hourly intervals.

9. Cytarabine 2000mg/ m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 180 minutes twice a day

Administration instructions

Cytarabine doses are to be given at 12 hour intervals

10. Etoposide 60mg/ m^2 intravenous infusion in 500ml sodium chloride 0.9% over 60 minutes

11. Mesna 300mg/ m^2 intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes

12. Warning – Ifosfamide and Mesna Combination Bag

Administration Instructions

The ifosfamide is mixed in the same infusion bag as the mesna.

13. Ifosfamide 1500mg/m² and mesna 1500mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Administration Instructions

The ifosfamide and mesna are mixed in the same infusion bag of 1000ml sodium chloride 0.9%.

14. Mesna 900mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours

Administration instructions

Starting immediately after the ifosfamide/mesna

Day 2

15. 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, days 1 to 7 days then as required oral or intravenous
3. Ondansetron 8mg twice a day, days 1 to 7 oral or intravenous
4. Prednisolone 0.5% or dexamethasone 0.1% eye drops one drop into both eyes four times a day, days 1 to 4
5. Growth factor continued until the neutrophil count is above $1 \times 10^9/L$
 - filgrastim or bioequivalent 30 million units once a day from day 7 subcutaneous
 - lenograstim or bioequivalent 33.6million units once a day from day 7 subcutaneous
 - pegfilgrastim or bioequivalent 6mg once only on day 7 subcutaneous
6. Folinic acid 15mg four times a day for one day starting 24 hours after the administration of intrathecal methotrexate (normally day 6)
7. Aciclovir 400mg oral twice a day
8. Pentamidine 300mg nebule once a month
9. Fluconazole 50mg once a day
10. Consider gastric protection
11. Consider mouthwashes
12. Consider norethisterone for menstruating women
13. Consider pethidine 25-50mg intravenous bolus for rituximab related rigors unresponsive to corticosteroids

16. Warning – Cytarabine is TWICE a day

Administration Instructions

The cytarabine is to be given twice a day at twelve hourly intervals.

17. Cytarabine 2000mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 180 minutes twice a day

Administration instructions

Cytarabine doses are to be given at 12 hour intervals

18. Etoposide 60mg/m² intravenous infusion in 500ml sodium chloride 0.9% over 60 minutes

19. Mesna 300mg/m² intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes

20. Warning – Ifosfamide and Mesna Combination Bag

Administration Instructions

The ifosfamide is mixed in the same infusion bag as the mesna.

21. Ifosfamide 1500mg/m² and mesna 1500mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Administration Instructions

The ifosfamide and mesna are mixed in the same infusion bag of 1000ml sodium chloride 0.9%

22. Mesna 900mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours

Administration instructions

Starting immediately after the ifosfamide/mesna

Day 3, 4

23. 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, days 1 to 7 days then as required oral or intravenous
3. Ondansetron 8mg twice a day, days 1 to 7 oral or intravenous
4. Prednisolone 0.5% or dexamethasone 0.1% eye drops one drop into both eyes four times a day, days 1 to 4
5. Growth factor continued until the neutrophil count is above $1 \times 10^9/L$
 - filgrastim or bioequivalent 30 million units once a day from day 7 subcutaneous
 - lenograstim or bioequivalent 33.6 million units once a day from day 7 subcutaneous
 - pegfilgrastim or bioequivalent 6mg once only on day 7 subcutaneous
6. Folinic acid 15mg four times a day for one day starting 24 hours after the administration of intrathecal methotrexate (normally day 6)
7. Aciclovir 400mg oral twice a day
8. Pentamidine 300mg nebule once a month
9. Fluconazole 50mg once a day
10. Consider gastric protection
11. Consider mouthwashes
12. Consider norethisterone for menstruating women
13. Consider pethidine 25-50mg intravenous bolus for rituximab related rigors unresponsive to corticosteroids

24. Etoposide $60\text{mg}/\text{m}^2$ intravenous infusion in 500ml sodium chloride 0.9% over 60 minutes

25. Mesna $300\text{mg}/\text{m}^2$ intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes

26. Warning – Ifosfamide and Mesna Combination Bag

Administration Instructions

The ifosfamide is mixed in the same infusion bag as the mesna.

27. Ifosfamide $1500\text{mg}/\text{m}^2$ and mesna $1500\text{mg}/\text{m}^2$ intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Administration Instructions

The ifosfamide and mesna are mixed in the same infusion bag of 1000ml sodium chloride 0.9%

28. Mesna $900\text{mg}/\text{m}^2$ intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours

Administration instructions

1. Starting immediately after the ifosfamide/mesna

Day 5

29. 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, days 1 to 7 days then as required oral or intravenous
3. Ondansetron 8mg twice a day, days 1 to 7 oral or intravenous
4. Prednisolone 0.5% or dexamethasone 0.1% eye drops one drop into both eyes four times a day, days 1 to 4
5. Growth factor continued until the neutrophil count is above $1 \times 10^9/L$
 - filgrastim or bioequivalent 30 million units once a day from day 7 subcutaneous
 - lenograstim or bioequivalent 33.6 million units once a day from day 7 subcutaneous
 - pegfilgrastim or bioequivalent 6mg once only on day 7 subcutaneous
6. Folinic acid 15mg four times a day for one day starting 24 hours after the administration of intrathecal methotrexate (normally day 6)
7. Aciclovir 400mg oral twice a day
8. Pentamidine 300mg nebule once a month
9. Fluconazole 50mg once a day
10. Consider gastric protection
11. Consider mouthwashes
12. Consider norethisterone for menstruating women
13. Consider pethidine 25-50mg intravenous bolus for rituximab related rigors unresponsive to corticosteroids

30. Etoposide $60\text{mg}/\text{m}^2$ intravenous infusion in 500ml sodium chloride 0.9% over 60 minutes

31. Mesna $300\text{mg}/\text{m}^2$ intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes

32. Warning – Ifosfamide and Mesna Combination Bag

Administration Instructions

The ifosfamide is mixed in the same infusion bag as the mesna.

33. Ifosfamide 1500mg/m² and mesna 1500mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Administration Instructions

The ifosfamide and mesna are mixed in the same infusion bag of 1000ml sodium chloride 0.9%

34. Mesna 900mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours

Administration instruction

Starting immediately after the ifosfamide/mesna. This infusion may be replaced with oral mesna at a dose of 360mg/m² rounded upwards to the nearest 400mg capsule, at 0, 2 and 6 hours post ifosfamide infusion.

35. Warning – Intrathecal

Administration Instructions

Methotrexate 12.5mg intrathecal is due on day 5 of the cycle. This must be prescribed on an intrathecal chart to comply with national guidance. Ensure Folinic acid 15mg four times a day for one day starting 24 hours after the administration of intrathecal methotrexate. This warning is a reminder, not a prescription.

Day 7 and 9

36.Warning – CNS disease - Intrathecal cycle 1 only

Administration Instructions

For patients presenting with CNS disease please prescribe cytarabine 70mg intrathecal at cycle 1 only . Intrathecal chemotherapy must be prescribed on an intrathecal chart to comply with national guidance. This warning is a reminder, not a prescription.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	February 2018	Warnings added to regimen summary in terms of cytarabine twice a day, cyclophosphamide and mesna combinations and intrathecal agents. National dose bands added Growth factor units changed Header changed Toxicities removed Hepatic impairment guidance updated Admin instructions for hydrocortisone pre med removed Metoclopramide dose and duration updated "Bolus" removed from "intravenous bolus" for supportive medication throughout text Mucositis recommendation changed "according to local practice" and "oral" added to folinic acid instructions following intrathecal methotrexate CSCCN agreed bands removed Cytarabine infusion changed to 1000ml Etoposide changed to 500ml Disclaimer added	Dr Deborah Wright Pharmacist	Harriet Launders Pharmacist
1	August 2012	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Alison Milne Consultant Haematologist Dr Andrew Davies Consultant Medical Oncologist