

(R) CODOX M / (R) IVAC**Indication**

Burkitt's or Burkitt's-like lymphoma, especially those with 1 or more of the following poor risk criteria:

- Raised LDH level
- WHO performance status 2-4
- Ann Arbor stage III-IV
- More than 1 extra-nodal site
- Tumour mass ≥ 10 cm diameter

Lymphoblastic lymphoma, especially B subtype.

ICD-10 codes

C83.7

Regimen details**(R) CODOX-M (patients aged ≤ 65 years)**

Day	Drug	Dose	Route
0 or 1 and 10	Rituximab*	375mg/m ²	IV infusion
1 and 8	Vincristine	1.4mg/m ² (maximum dose 2mg)	IV infusion
1	Doxorubicin	40mg/m ²	IV bolus
1	Cyclophosphamide	800mg/m ²	IV infusion
2-5	Cyclophosphamide	200mg/m ²	IV infusion
0 or 2 and 4	Cytarabine	70mg	Intrathecal
10	Methotrexate	300mg/m ²	IV infusion
10	Methotrexate	2700mg/m ²	IV infusion
11	Calcium folinate	15mg/m ² 3 hourly for 12 hours starting 36 hours after start of methotrexate, then 6 hourly until serum methotrexate level $< 0.1\mu\text{mol/L}$	IV/PO
13	GCSF (as per local policy)	Daily until neutrophils $> 1.0 \times 10^9/\text{L}$	SC
15	Methotrexate	12.5mg	Intrathecal
16	Calcium folinate	15mg	PO

* if appropriate

(R) CODOX-M (patients aged > 65 years)

Day	Drug	Dose	Route
0 or 1 and 10	Rituximab*	375mg/m ²	IV infusion
1 and 8	Vincristine	1.4mg/m ² (maximum dose 2mg)	IV infusion
1	Doxorubicin	40mg/m ²	IV bolus
1	Cyclophosphamide	800mg/m ²	IV infusion
2-5	Cyclophosphamide	200mg/m ²	IV infusion
0 or 2 and 4	Cytarabine	70mg	Intrathecal
10	Methotrexate	100mg/m ²	IV infusion
10	Methotrexate	900mg/m ²	IV infusion
11	Calcium folinate	15mg/m ² 3 hourly for 12 hours starting 36 hours after start of methotrexate, then 6 hourly until serum methotrexate level <0.1µmols/L	IV/PO
13	GCSF (as per local policy)	Daily until neutrophils >1.0 x 10 ⁹ /L	SC
15	Methotrexate	12.5mg	Intrathecal
16	Calcium folinate	15mg	PO

* if appropriate

(R) IVAC (patients aged ≤ 65 years)

Day	Drug	Dose	Route
1 and 10	Rituximab*	375mg/m ²	IV infusion
1 - 5	Etoposide	60mg/m ²	IV infusion
1 - 5	Mesna	300mg/m ²	IV bolus
1 - 5	Ifosfamide and Mesna	1500mg/m ² and 1500mg/m ²	IV infusion
1 - 5	Mesna	900mg/m ²	IV infusion
1 and 2	Cytarabine	2g/m ² every 12 hours (total 4 doses)	IV infusion
5	Methotrexate	12.5mg	Intrathecal
6	Calcium folinate	15mg	PO
7	GCSF (as per local policy)	Daily until neutrophils >1.0 x 10 ⁹ /L	SC

* if appropriate

Prednisolone 0.5% eye drops QDS for 5-7 days.

(R) IVAC (patients aged > 65 years)

Day	Drug	Dose	Route
1 and 10	Rituximab*	375mg/m ²	IV infusion
1 - 5	Etoposide	60mg/m ²	IV infusion
1 - 5	Mesna	200mg/m ²	IV bolus
1 - 5	Ifosfamide and Mesna	1000mg/m ² and 1000mg/m ²	IV infusion
1 - 5	Mesna	600mg/m ²	IV infusion
1 and 2	Cytarabine	1g/m ² every 12 hours (total 4 doses)	IV infusion
5	Methotrexate	12.5mg	Intrathecal
6	Calcium folinate	15mg	PO
7	GCSF (as per local policy)	Daily until neutrophils >1.0 x 10 ⁹ /L	SC

* if appropriate

Prednisolone 0.5% eye drops QDS for 5-7 days.

Cycle frequency

Low risk

i.e. at least 3 of the factors below:

- Normal LDH level
- WHO performance status 0-1
- Ann Arbor stage I-II
- Number of extra-nodal sites (e.g. bone marrow, GI tract, CNS) ≤ 1

Three cycles of (R) CODOX-M (doses must be modified if age > 65 years)

High risk

i.e. all remaining patients are high risk. They should have 2 or more of the following factors:

- Raised LDH level
- WHO performance status 2-4
- Ann Arbor stage III-IV
- Number of extra-nodal sites >1

Two alternating cycles of each regimen is given (R) CODOX-M → (R) IVAC → (R) CODOX-M → (R) IVAC (doses must be modified if age > 65 years).

Each cycle is started as soon as possible after neutrophils have regenerated to $> 1.0 \times 10^9/L$ and platelets (unsupported) to $> 75 \times 10^9/L$.

Number of cycles

See above

Administration

Prior to chemotherapy:

Commence IV hydration of $4.5L/m^2/24$ hours or as close as is tolerated (ideally at least $3.0L/m^2/day$), with a sodium content of $\geq 75mmol/L$. Aim for diuresis of $150mL/hour$.

Furosemide should be used as required to maintain urine output.

Do not give potassium supplements unless serum potassium falls below $3.0mmol/L$.

Add sodium bicarbonate (start with $50mmol$ of sodium bicarbonate per litre) if the patient has a raised serum uric acid level. Maintain urine pH ≥ 7.0 (by increasing the amount of sodium bicarbonate in the infusion fluids to $100mmols/L$, if necessary). Stop adding bicarbonate to infusions when uric acid is back within the normal range, or serum bicarbonate $>30mmol/L$ and/or immediately prior to commencement of chemotherapy.

Rasburicase $0.2mg/kg$ for 5 - 7 days is highly recommended. Rasburicase is administered in $50mL$ sodium chloride 0.9% over 30 minutes. Alternatively allopurinol $10mg/kg/day$ in 2-3 divided doses for 3 days, reduced to $5mg/kg/day$ for the next 14 days must be prescribed.

Discontinue sodium bicarbonate prior to commencing chemotherapy.

(R) CODOX M

Rituximab is administered in $500mL$ sodium chloride 0.9% . The first infusion should be initiated at $50mg/hour$ and if tolerated the rate can be increased at $50mg/hour$ every 30 minutes to a maximum of $400mg/hour$. Subsequent infusions should be initiated at $100 mg/hour$ and if tolerated increased at $100mg/hour$ increments every 30 minutes to a maximum of $400 mg/hour$.

Vincristine is administered in $50mL$ sodium chloride 0.9% over 10 minutes, as per national guidance. Nurse to remain with patient throughout infusion.

Doxorubicin is administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%.

On day 1 **cyclophosphamide** is administered as IV infusion in 250-500mL sodium chloride 0.9% over 15-30 minutes. On days 2-5 cyclophosphamide is administered in 100-250mL sodium chloride 0.9% over 15-30 minutes.

Cytarabine is administered as per local guidelines for intrathecal chemotherapy. In accordance with the local trust policies, intrathecal cytarabine will not be released for administration until written confirmation is given that the IV cyclophosphamide has been administered.

Methotrexate pre and post hydration:

1000mL sodium chloride 0.45%/dextrose 5% with 20mmol potassium chloride and 50mmol sodium bicarbonate should be commenced 8-24 hours prior to methotrexate at a suggested rate of 1000mL over 4 hours and continued concurrently during methotrexate infusion and until calcium folinate rescue is no longer required.

Full dose methotrexate should only be given in the presence of a normal serum creatinine and $\text{CrCl} \geq 80\text{mL/min}$. See below for dose reductions in renal impairment.

Commence methotrexate regardless of blood counts.

Prior to commencing methotrexate, patients must have a urine pH ≥ 7.0 and a urine output $\geq 100\text{mL/hour}$. This should be maintained during treatment and until calcium folinate rescue is no longer required. Fluid balance should be closely monitored and urine pH measured hourly. Additional sodium bicarbonate (either added to fluids or given orally) may be required to maintain urine pH ≥ 7.0 .

Methotrexate is given in 2 separate doses. Methotrexate 300mg/m^2 (or 100mg/m^2) is administered in 250mL sodium chloride 0.9% over 60 minutes and the 2700mg/m^2 (or 900mg/m^2) dose is administered in 1000mL sodium chloride 0.9% over 23 hours.

Stop infusion at 24 hours regardless of dose given.

Calcium folinate is commenced 36 hours after the start of the methotrexate infusion and then every 3 hours for the next 12 hours (i.e. to give a total of 5 doses between 36 – 48 hours). It is administered as an IV bolus or IV infusion in 100mL glucose 5% over 30 minutes. Calcium folinate is then given every 6 hours until serum methotrexate level $<0.1\mu\text{mol/L}$. It may be given orally after the first 24 hours if the patient is compliant, not vomiting and otherwise without complication. Calcium folinate is available as 15mg and 30mg tablets.

Serum methotrexate levels should be taken 48 hours after the start of the methotrexate infusion and then every 24 hours. If the 48 hour level is $>2.0\mu\text{mol/L}$ the dose of calcium folinate should be doubled. Serum methotrexate levels and U+Es must be checked every 24 hours and urine output and pH every hour. Calcium folinate rescue and urine pH should be maintained ≥ 7.0 until the methotrexate level is $<0.1\mu\text{mol/L}$. The dose of calcium folinate should also be increased if serum creatinine increases $> 50\%$ from baseline.

(R) IVAC

Rituximab is administered in 500mL sodium chloride 0.9%. If the previous first dose of rituximab has been well tolerated the infusion should be initiated at 100mg/hour and if tolerated increased at 100mg/hour increments every 30 minutes to a maximum of 400mg/hour.

Etoposide is administered in 500-1000mL (concentration dependent) sodium chloride 0.9% over 60 minutes.

Mesna is administered as a bolus or IV infusion over 15 minutes prior to ifosfamide. Ifosfamide is then administered with mesna (in the same bag) in 500mL sodium chloride 0.9% over 60 minutes. This is followed by mesna in 500mL sodium chloride 0.9% administered over 12 hours.

Cytarabine is administered in 1000mL sodium chloride 0.9% over 3 hours every 12 hours on days 1 and 2. A total of 4 doses are given.

Methotrexate is administered as per local guidelines for intrathecal chemotherapy. In accordance with the local trust policies, intrathecal methotrexate will not be released for administration until written confirmation is given that the IV chemotherapy has been administered.

Pre-medication

Antiemetics as per local policy.

Rituximab premedication:

- Paracetamol 1g PO 60 minutes prior to rituximab infusion
- Chlorphenamine 10mg IV bolus 15 minutes prior to rituximab infusion
- Dexamethasone 8mg IV bolus or hydrocortisone 100mg IV bolus 15 minutes prior to rituximab infusion (may be omitted if day 1 prednisolone 100mg PO has been taken at least 30 minutes prior to the start of the rituximab infusion)

Emetogenicity

(R) CODOX M has high emetic potential on day 1 and moderate on days 8 and 10.

(R) IVAC has very high emetic potential on days 1-5.

Additional supportive medication

Rasburicase or allopurinol as appropriate (see above)

Mouthwashes as per local policy

H₂ antagonist or PPI as per local policy

Antibacterial prophylaxis as per local policy

(R) CODOX-M:

Fluconazole 50-100mg OD (Note - caution with vincristine because of risk of peripheral neuropathy)

(R) IVAC:

Itraconazole 2.5mg/kg BD

Prednisolone 0.5% eye drops QDS (to avoid chemical conjunctivitis from high-dose cytarabine)

Extravasation

Doxorubicin and vincristine are vesicant (Group 5)

Rituximab, cytarabine, ifosfamide and cyclophosphamide are neutral (Group 1)

Methotrexate and etoposide are inflammatant (Group 2)

Investigations – pre first cycle

Investigation	Validity period (or as per local policy)
FBC (with film)	72 hours
U+E (including creatinine)	72 hours
LFTs	72 hours
Uric acid	72 hours
Calcium	72 hours
Magnesium	72 hours
Phosphate	72 hours

An HIV test should be carried out as Burkitt's lymphoma is one of the most common histological subtypes seen in HIV-positive patients. Hepatitis B and C serology should also be carried out.

Other pre-treatment investigations:

Immunoglobulin levels

Bone marrow aspirate and trephine biopsy

If clinical suspicion of cardiac dysfunction: ECHO and/or MUGA

Formal renal function measurement, prior to high dose methotrexate.

Investigations – pre subsequent cycles

Investigation	Validity period (or as per local policy)
FBC	Daily during chemotherapy then 3 times a week
U+E (including creatinine)	Daily during chemotherapy then 3 times a week
LFTs	Daily during chemotherapy then 3 times a week
Uric acid	Daily during chemotherapy then 3 times a week
Calcium	Daily during chemotherapy then 3 times a week
Magnesium	Daily during chemotherapy then 3 times a week
Phosphate	Daily during chemotherapy then 3 times a week

Serum methotrexate levels, as above.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	$> 1.0 \times 10^9/L$
Platelets	$> 75 \times 10^9/L$
Creatinine Clearance (CrCl)	≥ 80 mL/min
Bilirubin	\leq ULN
AST/ALT	\leq ULN

Dose modifications

- Haematological toxicity**

If neutrophils $\leq 1.0 \times 10^9/L$ and/or platelets $\leq 75 \times 10^9/L$ delay until recovery.

- Renal impairment**

Renal outflow obstruction and/or uric acid nephropathy are not uncommon. In these circumstances, more conventional chemotherapy +/- haemodialysis or the insertion of nephrostomy tubes are recommended to obtain initial control of the lymphoma and allow improved renal function before commencing (R) CODOX-M.

CrCl (mL/min)	Methotrexate dose	Etoposide dose	Ifosfamide dose	Cytarabine dose
≥ 80	100%	100%	100%	100%
60-79	65%			
50-59	50%	75%	70%	60%
45-49				
40-44	50%	50%	Consultant decision	50%
30-39				
<30	Discontinue	50% (if CrCl < 15 mL/min)		Discontinue

CrCl (mL/min)	Cyclophosphamide dose
>20	100%
10-20	75%
< 10	50%

Doxorubicin is mainly metabolised by the liver. Consultant decision in severe renal impairment.
 Vincristine – no dose reduction required.

• **Hepatic impairment**

Bilirubin (x ULN)		AST/ALT (x ULN)	Doxorubicin dose
< 1	And	< 2	100%
< 1	And	2-3	75%
1-2.5	Or	> 3	50%
2.5- 4			25%
> 4			Omit

Bilirubin (x ULN)		AST/ALT (x ULN)	Vincristine dose
< ULN	And	≤ 2	100%
1 – 2.5	Or	> 3	50%
> 2.5	And	< ULN	50%
> 2.5	And	> 3	Omit

Ifosfamide is contraindicated if bilirubin > ULN or AST/ALT > 2.5 x ULN.

Cyclophosphamide is not recommended if bilirubin > 1.5 x ULN or AST/ALT > 3 x ULN (consultant decision).

Cytarabine dose should be reduced to 50% if bilirubin > 1.5 x ULN. Doses may be escalated in subsequent cycles in the absence of toxicity (consultant decision).

Evidence for etoposide dose modification in hepatic impairment is variable. If bilirubin 1-2.5 x ULN or AST/ALT 1-3 x ULN consider 50% dose. If bilirubin > 2.5 x ULN or AST/ALT > 3 x ULN consultant decision.

• **Other toxicities**

Neurotoxicity: monitor for signs of peripheral sensory loss or constipation. Discuss with the consultant and consider dose reducing vincristine or switching to vinblastine. If grade 3-4 discontinue vincristine. Discuss with consultant.

If previous or existing cardiac history, consider omitting doxorubicin. Consultant decision.

If CNS involvement at diagnosis:

Intensified CNS chemotherapy treatment is as per table below, regardless of age, and is given for THE FIRST TWO CYCLES ONLY.

(R) CODOX M

Day	Drug	Intrathecal Dose	Intraventricular Dose (Ommaya reservoir)
2, 4, 6	Cytarabine	70mg	15mg
15, 17	Methotrexate*	12.5mg	2mg

*calcium folinate 15mg PO to be given on day 16 and 18, 24 hours after intrathecal methotrexate.

(R) IVAC

Day	Drug	Intrathecal Dose	Intraventricular Dose (Ommaya reservoir)
5	Methotrexate*	12.5mg	2mg
7, 9	Cytarabine	70mg	15mg

*calcium folinate 15mg PO to be given on day 6, 24 hours after intrathecal methotrexate.

Adverse effects - for full details consult product literature/ reference texts**• Serious side effects**

Secondary malignancy
Severe myelosuppression
Infertility/Early menopause
Tumour lysis syndrome
Cardiotoxicity
Neurotoxicity
Acute pulmonary toxicity
Nephrotoxicity
Hepatotoxicity

• Frequently occurring side effects

Diarrhoea
Fatigue
Nausea and vomiting
Myelosuppression
Alopecia
Mucositis
Peripheral neuropathy
Conjunctivitis (cytarabine)
Headache (intrathecal chemotherapy)

• Other side effects

Fluid retention
Haemorrhagic cystitis
Rash
Jaw pain
Red coloured urine (doxorubicin – for up to 24 hours following administration)

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Vincristine:

Itraconazole, voriconazole, posaconazole: increase severity of neuromuscular side effects. Avoid for 72 hours either side of vincristine dose if concurrent use cannot be avoided.

Cyclophosphamide:

Amiodarone: increased risk of pulmonary fibrosis – avoid if possible

Clozapine: increased risk of agranulocytosis – avoid concomitant use

Digoxin tablets: reduced absorption – give as liquid form

Indapamide: prolonged leucopenia is possible - avoid

Itraconazole: may increase adverse effects of cyclophosphamide

Phenytoin: reduced absorption - may need to increase dose of phenytoin

Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Ifosfamide:

Nephrotoxic agents: enhanced nephrotoxic effects

Aprepitant: increased risk of ifosfamide neurotoxicity

Inhibitors of CYP 3A4 (including ketoconazole, fluconazole, itraconazole): reduced activation and metabolism of ifosfamide – altered efficacy and increased CNS and nephrotoxicity.

Enzyme inducers (including carbamazepine, corticosteroids, phenytoin, St John Wort) – increased toxicity

Antidiabetic agents (including sulphonylureas): enhanced antidiabetic effect

Allopurinol: theoretical increased risk of bone marrow depression

Methotrexate:

Avoid all nephrotoxic agents

NSAIDs: increase risk of methotrexate toxicity – avoid

Omeprazole: potential to increase methotrexate levels

Co-trimoxazole: if used concurrently may cause severe bone marrow depression – avoid

Theophylline: may reduce theophylline clearance – avoid

Acetretin: increased risk of hepatitis

Cytarabine:

Digoxin: cytarabine may affect plasma digoxin levels – consider monitoring

Additional comments

Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Doxorubicin has a life time maximum cumulative dose of 450mg/m²

References

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