# (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 ≥10cm 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 <0.1µmols/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

# if for intraventricular administration via Ommaya reservoir reduced doses are used, refer to CNS involvement section below for dosing.

**(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

# if for intraventricular administration via Ommaya reservoir reduced doses are used, refer to CNS involvement section below for dosing.

**(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

# if for intraventricular administration via Ommaya reservoir reduced doses are used, refer to CNS involvement section below for dosing.

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

# if for intraventricular administration via Ommaya reservoir reduced doses are used, refer to CNS involvement section below for dosing.

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

**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.

## 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 x 10$^9$/L and platelets (unsupported) to > 75 x 10$^9$/L.

## Number of cycles

See above

## Administration

**Prior to chemotherapy:**

Commence IV hydration of 4.5L/m²/24 hours or as close as is tolerated (ideally at least 3.0L/m²/day), with a sodium content of ≥ 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 CrCl ≥ 80mL/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 ≥ 100mL/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 <0.1µmols/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 >2.0µmols/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 <0.1µmols/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
$H_2$ 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 for 5-7 days(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 x $10^9$/L |
| Platelets | > 75 x $10^9$/L |
| Creatinine Clearance (CrCl) | ≥ 80 mL/min |
| Bilirubin | ≤ ULN |
| AST/ALT | ≤ ULN |

## Dose modifications

- **Haematological toxicity**

If neutrophils ≤ 1.0 x $10^9$/L and/or platelets ≤ 75 x $10^9$/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% | | 70% | 60% |
| 45-49 | | 75% | | |
| 40-44 | 50% | | | 50% |
| 30-39 | | | Consultant decision | |
| <30 | Discontinue | 50% (if CrCl < 15mL/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.

## 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/$m^2$

## References


- Summary of Product Characteristics Vincristine (Hospira) accessed 24 July 2014 via www.medicines.org.uk
- Summary of Product Characteristics Doxorubicin (Hospira) accessed 24 July 2014 via www.medicines.org.uk
- Summary of Product Characteristics Etoposide (Medac) accessed 24 July 2014 via www.medicines.org.uk
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- Summary of Product Characteristics Cyclophosphamide accessed 24 July 2014 via http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs
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