R-IDARAM

Indication
Secondary CNS lymphoma

ICD-10 codes
Codes with a prefix C85

Regimen details

Day	Drug	Dose	Route
1	Rituximab	375mg/m^2	IV infusion
1	**Methotrexate**	**12.5mg**	**Intrathecal**
1	**Cytarabine**	**70mg**	**Intrathecal**
2, 3 and 4	Dexamethasone	100mg	IV infusion
2 and 3	Idarubicin	10mg/m^2	Slow IV bolus
2 and 3	Cytarabine	1000mg/m^2	IV infusion
4	Methotrexate	2g/m^2	IV infusion
5 onwards	Calcium folinate	15mg/m^2 (see below)	IV/PO
8	GCSF (as per local policy)	Daily until neutrophils > 1.0 x 10^9/L	SC
9	**Methotrexate**	**12.5mg**	**Intrathecal**
9	**Cytarabine**	**70mg**	**Intrathecal**

Prednisolone 0.5% eye drops QDS days 2-8.

Cycle frequency
21 days

Number of cycles
4 cycles with restaging after 2 cycles

Administration
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 by 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.

Dexamethasone is administered as an IV infusion in 100mL sodium chloride 0.9% over 30 minutes.

Idarubicin is administered as a slow bolus over 5-10 minutes via a fast running drip.

Intravenous cytarabine is administered in 250mL sodium chloride 0.9% over 60 minutes.

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.

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.

Intravenous methotrexate is administered in 1000mL sodium chloride 0.9% over 3 hours.

Calcium folinate is commenced 24 hours after the start of the first methotrexate infusion at a dose of 15mg/m^2 every 3 hours for 6-8 doses. 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.

Intrathecal cytarabine and methotrexate should be administered as per national guidance and local trust policy.

Pre-medication

Rituximab premedication:

- Paracetamol 1g PO 60 minutes prior to rituximab
- Chlorphenamine 10mg IV bolus 15 minutes prior to rituximab
- Dexamethasone 8mg IV bolus or hydrocortisone 100mg IV bolus 15 minutes prior to rituximab

Emetogenicity

This regimen has high emetic potential

Additional supportive medication

Allopurinol 300mg (100mg if creatinine clearance <20ml/min) OD for the first cycle.
Aciclovir prophylaxis as per local policy
PCP prophylaxis dapsone 100mg OD throughout treatment or co-trimoxazole after methotrexate clearance.
Mouthwashes as per local policy
H_2 antagonist or PPI as per local policy
Antibacterial prophylaxis as per local policy
Consider antifungal prophylaxis as per local policy
GCSF from day 8 until neutrophils >1.0 x10^9/L
Prednisolone 0.5% eye drops QDS days 2-8.

Extravasation

Idarubicin is vesicant (Group 5)
Rituximab and cytarabine are neutral (Group 1)
Methotrexate is inflammatant (Group 2)

Investigations – pre first cycle

Investigation	Validity period
FBC	7 days
U + E (including creatinine)	7 days
LFTs	7 days
LDH	7 days
Glucose	7 days

Other investigations:
Hepatitis B and C serology
HIV serology
If clinical suspicion of cardiac dysfunction, cardiac history or in patient ≥ 65 years: ECHO and/or MUGA
Formal renal function measurement (EDTA or 24 hour urine collection as per local policy), prior to high dose methotrexate.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+Es (including creatinine)	7 days
LFTs	7 days
LDH	7 days
Glucose	If clinically indicated

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
CrCl	> 80mL/min
Bilirubin	≤ 1.5 x ULN
AST/ALT	≤ 3 x ULN

Dose modifications

- **Haematological toxicity**

There should be no dose modifications for haematological parameters for the first cycle.
If neutrophils <1.0 x 10^9/L and/or platelets <75 x 10^9/L delay subsequent cycles by one week.

- **Renal impairment**

CrCl (mL/min)	**Intravenous methotrexate dose**	**Intravenous cytarabine dose**
≥ 80	100%	100%
60-80	50%	100%
50-60	50%	60%
46-50	Omit	60%
31-45		50%
< 30		Omit

Creatinine (µmol/L)	**Idarubicin dose**
<99	100%
100-174	50%
>175	Omit

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Methotrexate dose**	**Cytarabine dose**
≤ 1.5	and	≤ 3	100%	100%
1.5 – 3	and	≤ 3	100%	50%
3 – 5	or	> 3	75%	50%
> 5			Discontinue	50%

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).

Note: raised transaminases and/or bilirubin may occur for up to 2 weeks after methotrexate.

Bilirubin (x ULN)	**Idarubicin dose**
< 1.5	100%
1.5-2	50%
>2	omit

- **Other toxicities**

Neurotoxicity:
Cytarabine may cause cerebral and cerebellar toxicity.

Toxicity	**Definition**	**Methotrexate**	**Cytarabine**
Cardiovascular	Grade 3-4	Interrupt treatment until resolved	Interrupt treatment until resolved
Coagulation	Grade 4	75% dose	75% dose
Gastrointestinal	Grade 4	75% dose	75% dose
Pulmonary	Grade 4	75% dose	75% dose

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Cardiotoxicity
Gastrointestinal bleeding
Neurotoxicity
Nephrotoxicity
Acute pulmonary toxicity
Hepatotoxicity
CNS toxicity (cytarabine)
Infertility

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis
Tumour lysis syndrome
Diarrhoea
Fatigue
Alopecia
Conjunctivitis (cytarabine)

- **Other side effects**

Haemorrhagic cystitis
Cytarabine syndrome (fever, myalgia, rash)

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

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Methotrexate:
Avoid all nephrotoxic agents
NSAIDS (including **aspirin)**: increase risk of methotrexate toxicity – avoid, discontinue at least 72 hours before methotrexate and do not recommence until methotrexate level less than 0.1 µmol/L.
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
Penicillins: may reduce excretion of methotrexate levels
Aminoglycosides

Cytarabine:
Digoxin: cytarabine may affect plasma digoxin levels – consider monitoring

Idarubicin:
Cardiotoxic drugs: avoid concomitant use
Cyclosporin A: may increase idarubicin levels

Additional comments

References

- Summary of Product Characteristics Methotrexate (Hospira) accessed 16 September 2015 via www.medicines.org.uk
- Summary of Product Characteristics Cytarabine (Pfizer) accessed 16 September 2015 via www.medicines.org.uk
- Summary of Product Characteristics Idarubicin (Pfizer) accessed 16 September 2015 via www.medicines.org.uk
- Summary of Product Characteristics Rituximab (Roche) accessed 16 September 2015 via www.medicines.org.uk
- BCSH guidelines on the diagnosis and management of adult patients with primary CNS lymphoma (PCNSL) and primary intra-ocular lymphoma (PIOL)
- Maciocia, Badat, Cheesman et al. Treatment of Non-Hodgkin's lymphoma with secondary CNS involvement: encouraging response rates using CNS-penetrating Idaram chemotherapy (2013) Blood 122; 4367
- Moreton P, Morgan GJ, Gilson D, Smith GM, et al. The development of targeted chemotherapy for CNS lymphoma- a pilot study for the IDARAM regimen. Cancer Chemother.Pharmacol 2004; 53: 324-328.

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