Dose adjusted (DA)-EPOCH-R

Indication

High-risk CD20+ diffuse large B cell lymphoma especially C-MYC and BCL-2 activated (i.e. 'double hit' lymphoma) and mediastinal sclerosing (thymic) large B cell lymphoma.

ICD-10 code

C83.3, C85.2

Regimen details

This regimen is essentially a variation of R-CHOP with added etoposide.

EPOCH-R cycle 1

Days	Drug	Dose	Route
1-5	Prednisolone	60mg/m^2 **BD**	PO
1	Rituximab	375mg/m^2	IV infusion
1-4	Doxorubicin	10mg/m^2/day	IV infusion
1-4	Vincristine	0.4mg/m^2/day	IV infusion
1-4	Etoposide	50mg/m^2/day	IV infusion
5	Cyclophosphamide	750mg/m^2	IV
6 onwards	GCSF (as per local policy)	Daily until neutrophils >1.0 x 10^9/L	SC

Doses should be based on actual body weight and should not be routinely capped.

For cycles 2-6 doses are adjusted according to full blood count monitoring in weeks 2 and 3 of the preceding cycle, see haematological dose modifications below.

Cycle frequency

21 days

Number of cycles

6-8 cycles, depending on response and tolerability:
As long as tolerated give 4 cycles of treatment then restage:

- If complete radiological response, give 2 further cycles, then stop.
- If progressive disease, switch to alternative treatment.
- If partial remission, continue with 2 further courses and restage. If good partial or complete response after 6 cycles, give 2 further cycles and then stop.

Maximum 8 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 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.

Doxorubicin, vincristine and etoposide are administered concurrently over 24 hours on days 1-4 as per local practice.

Day 5
Cyclophosphamide is administered in as a bolus or alternatively in 500mL sodium chloride 0.9% over 30 minutes.

Pre-medication

Patients with bulky disease may require pre-hydration with 1000mL sodium chloride 0.9% over 4-6 hours.
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 PO has been taken at least 30 minutes prior to the start of the rituximab infusion)

Emetogenicity

This regimen has moderate emetic potential

Additional supportive medication

Anti-emetics as per local policy
Allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for the first cycle only
Mouthwashes as per local policy
H_2 antagonist or PPI as per local policy
Aciclovir 400mg PO BD (or as per local policy) throughout treatment and for 3 months after completion.
Co-trimoxazole 480mg PO BD on Mondays, Wednesdays and Fridays (or as per local policy) throughout treatment and for 3 months after completion.
Fluconazole 50mg PO OD should be considered for the duration of treatment.
Mesna should be considered if level +2 doses of cyclophosphamide are prescribed following dose escalation.

Extravasation

Doxorubicin and vincristine are vesicant (Group 5)
Rituximab and cyclophosphamide are neutral (Group 1)
Etoposide is 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
Glucose	72 hours
Calcium	72 hours
Magnesium	72 hours
Phosphate	72 hours

Other pre-treatment investigations:
Immunoglobulin levels
Hepatitis B and C, EBV, CMV serology
Bone marrow aspirate and trephine biopsy
If clinical suspicion of cardiac dysfunction: ECHO and/or MUGA
Urine pregnancy test if appropriate

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	72 hours before treatment and twice weekly (see below)
U+E (including creatinine)	72 hours
LFTs	72 hours
Uric acid	72 hours
Glucose	72 hours
Calcium	72 hours
Magnesium	72 hours
Phosphate	72 hours

Standard limits for administration to go ahead

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelet count	≥ 75 x 10^9/L
CrCl	> 50mL/min
AST/ALT	< 2 x ULN
Bilirubin	< ULN

If blood results are not within range this may be due to marrow and/or splenic involvement by lymphoma and is still an indication to treat. In this situation, decisions on dose modifications and authorisation to proceed must be made by the consultant.

Dose modifications

- **Haematological toxicity**

If neutrophils ≤ 1.0 x 10^9/L and/or platelets ≤ 75 x 10^9/L discuss with consultant as above.

The cyclophosphamide, doxorubicin and etoposide doses for cycles 2 – 6 are adjusted according to the results of twice-weekly FBC obtained 3 days apart (i.e. on days 9, 12, 15, 18 - during weeks 2 and 3 of the preceding cycle).
If:

- Nadir neutrophils ≥ 0.5 x 10^9/L, increase by 1 dose level.
- Nadir neutrophils < 0.5 x 10^9/L on 1 or 2 measurements, maintain the same dose level.
- Nadir neutrophils < 0.5 x 10^9/L on at least 3 measurements, decrease by 1 dose level.

If platelet nadir < 25 x 10^9/L, reduce by 1 dose level regardless of neutrophil count.

Drug	**Dose level -2** (64%)	**Dose level -1** (80%)	**Dose level 0 (i.e. cycle 1) (100%)**	**Dose level +1** (120%)	**Dose level +2** (144%)
Etoposide (days 1-4)	32 mg/m^2/day	40 mg/m^2/day	**50 mg/m^2/day**	60 mg/m^2/day	72 mg/m^2/day
Doxorubicin (days 1-4)	6.4 mg/m^2/day	8 mg/m^2/day	**10 mg/m^2/day**	12 mg/m^2/day	14.4 mg/m^2/day
Cyclophosphamide (day 5)	480 mg/m^2	600 mg/m^2	**750 mg/m^2**	900 mg/m^2	1080 mg/m^2

Doses of rituximab, prednisolone and vincristine are not adjusted as above.

- **Renal impairment**

CrCl (mL/min)	**Etoposide dose**	**Cyclophosphamide dose**
> 50	100%	100%
20-50	75%	100%
15-20	75%	75%
10-14	50%	75%
<10	50%	50%

Subsequent doses should be based on clinical response.

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

Cyclophosphamide is not recommended if bilirubin > 1.5 x ULN or AST/ALT > 3 x ULN (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**

Cardiotoxicity:
Consider dose reduction of doxorubicin in the event of cardiac impairment (however, one of the aims of infusional doxorubicin is to lessen the incidence of cardiac toxicity by reducing peak levels of doxorubicin.)
If ejection fraction by transthoracic echocardiography < 40% omit doxorubicin and consider switching to alternative chemotherapy regimen.

Neurotoxicity:

Toxicity	**Definition**	**Vincristine dose**
Peripheral neuropathy	Grade 2	50%
	Grade 3-4	omit

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

- **Serious side effects:**

Myelosuppression
Cardiotoxicity
Infusion reactions (rituximab)

- **Frequently occurring side effects:**

Myelosuppression
Alopecia
Nausea and vomiting
Mucositis
Peripheral neuropathy
Diarrhoea
Constipation

- **Other side effects:**

Haemorrhagic cystitis
Rash
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.

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 4 March 2015 via www.medicines.org.uk
- Summary of Product Characteristics Doxorubicin (Hospira) accessed 4 March 2015 via www.medicines.org.uk
- Summary of Product Characteristics Etoposide (Medac) accessed 4 March 2015 via www.medicines.org.uk
- Summary of Product Characteristics Rituximab (Roche) accessed 4 March 2015 via www.medicines.org.uk
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- Wilson WH, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood. 2002 Apr 15;

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- Jermann M, et al. Rituximab-EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: results of a phase II study. Ann Oncol. 2004 Mar; 15(3): 511-6.

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