DA-EPOCH-R

INDICATION

High grade lymphoma.
Omit rituximab if CD20 negative.

NB. This version combines both previous inpatient and ambulatory protocols.
See **DRUG REGIMEN** section for details.

IMPORTANT: EXTRAVASATION RISK

IT MUST ONLY BE ADMINISTERED VIA CENTRAL VENOUS CATHETER.

TREATMENT INTENT

Curative

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease - PET-CT /CT scan with contrast (chest, abdomen and pelvis), presence or absence of B-symptoms, clinical extent of disease, consider bone marrow trephine.
3. Blood tests - FBC, DCT, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, β_2 microglobulin, hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save.
4. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
5. ECG +/- Echo - if clinically indicated.
6. Record performance status (WHO/ECOG).
7. Record height and weight.
8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
9. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice by referring to the Oxford Fertility Unit.
10. Hydration - in patients with bulky disease pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. Patients at high risk of tumour lysis refer to tumour lysis protocol.
11. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
12. Treatment should be agreed in the relevant MDT.
13. This chemotherapy regimen is usually delivered during an inpatient stay but can be used within the ambulatory setting for patient(s) meeting criteria. Refer to local Ambulatory Care Operational Policy.

ADMINISTERED VIA CENTRAL VENOUS CATHETER.

DRUG REGIMEN

NB: In this regimen ALL doses are based on true body weight and should not be routinely capped.

	Dose Level -2	**Dose Level -1**	**Dose Level 1 CYCLE 1**	**Dose Level 2**	**Dose Level 3**
	64% (80% x 0.8)	80% (100% x 0.8)	**100% starting dose**	120% (100% x 1.2)	144% (120% x 1.2)
Day 1 RITUXIMAB	375 mg/m^2/day IV infusion	375 mg/m^2/day IV infusion	**375 mg/m^2/day IV infusion**	375 mg/m^2/day IV infusion	375 mg/m^2/day IV infusion
Days 1 to 4 ETOPOSIDE*	50 mg/m^2/day IV infusion	50 mg/m^2/day IV infusion	**50 mg/m^2/day IV infusion**	60 mg/m^2/day IV infusion	72 mg/m^2/day IV infusion
Days 1 to 4 DOXORUBICIN*	10 mg/m^2/day IV infusion	10 mg/m^2/day IV infusion	**10 mg/m^2/day IV infusion**	12 mg/m^2/day IV infusion	14.4 mg/m^2/day IV infusion
Days 1 to 4 VINCRISTINE*	0.4 mg/m^2/day IV infusion	0.4 mg/m^2/day IV infusion	**0.4 mg/m^2/day IV infusion**	0.4 mg/m^2/day IV infusion	0.4 mg/m^2/day IV infusion
Days 1 to 5 PREDNISOLONE	60 mg/m^2 OD PO	60 mg/m^2 OD PO	**60 mg/m^2 OD PO**	60 mg/m^2 OD PO	60 mg/m^2 OD PO
Day 5 CYCLOPHOSPHAMIDE	480 mg/m^2/day IV bolus	600 mg/m^2/day IV bolus	**750 mg/m^2/day IV bolus**	900 mg/m^2/day IV bolus	1080 mg/m^2/day IV bolus
Day 6 G-CSF	As per local policy	As per local policy	**As per local policy**	As per local policy	As per local policy

*The administration of etoposide, doxorubicin and vincristine is dependent on whether the regimen is given as inpatient or ambulatory. See next section.

RITUXIMAB IV infusion on Day 1 in 500 mL sodium chloride 0.9%. Consider omitting rituximab in first cycle if bulky disease. (refer to rituximab protocol for titration of infusion rate).

PREDNISOLONE: give 1st dose before rituximab as pre-med. Available in 5 mg and 20 or 25mg tablets depending on local formulary, rounded to the nearest tablet size. Prednisolone dose was given as 60mg/m^2 BD in reference studies, but it has been agreed locally to reduce it to 60mg/m^2 OD due to patient tolerability.

G-CSF daily from day 6 and continue until ANC > 5 x 10^9/L (prescribe as per local policy).
Patients at risk of central nervous system disease should receive intrathecal chemotherapy +/- high dose Methotrexate at end of induction chemotherapy.

INPATIENT regimen (Etoposide/ Doxorubicin/ Vincristine)

ETOPOSIDE IV infusion in 500 mL sodium chloride 0.9% over 24 hours. Replace bag promptly daily for a continuous infusion over 96 hours.

DOXORUBICIN and VINCRISTINE are mixed together, made up to 48 mL with sodium chloride 0.9% IV infusion and administered via a LV infusor over 96 hours. **LV infusor must not be used in ambulatory basis.**

Consultant decision: In the event that a significant amount of vincristine (>15% dose) cannot be included in the pump /infusor due to high BSA and stability issue, the remaining vincristine (up to 1mg) can be administered as an IV infusion in 50mL sodium chloride 0.9% over 10 minutes on Day 5 after pump /infusor disconnection.

AMBULATORY regimen (Etoposide Phosphate/ Doxorubicin/ Vincristine)

If etoposide phosphate (Etopophos®) is available, selected patients suitable for ambulatory care may receive the combination as:

ETOPOSIDE PHOSPHATE (Etopophos®) , DOXORUBICIN and VINCRISTINE mixed together in 1000 mL sodium chloride 0.9% and infused over 48 hours with a CADD pump. The infusion bag is replaced on day 3 to complete the 96-hour infusion.

CYCLE FREQUENCY

Cycle repeats every 21 days.

RESTAGING

Give 4 courses and consider restaging with CT scan with contrast. If progressive disease consider other treatment. If remission, continue to 6-8 cycles in total and restage with PET-CT +/- Bone Marrow Trephine.

DOSE MODIFICATIONS

Haematological toxicity: proceed if pre-treatment ANC > 1.0 x 10^9/L and platelets > 75 x 10^9/L, otherwise recheck FBC daily until recovery - daily support with G-CSF as necessary.

Cyclophosphamide, Doxorubicin and Etoposide dose adjustment paradigm:
Dose on cycle 1 may be adjusted from cycle 2 as per results of TWICE-WEEKLY complete FBC obtained 3 days apart, e.g. days 9, 12, 15, 18. Dose adjustments apply to a whole treatment cycle and are based on neutrophil count at nadir of previous cycle.

- If nadir ANC ≥ 0.5 x 10^9/L, **increase by 1 dose level.**
- If nadir ANC < 0.5 x 10^9/L on 1 OR 2 measurements, **maintain the same dose level.**
- If nadir ANC < 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 ANC.

Note: Dose adjustments above starting dose level (level 1) apply to etoposide, doxorubicin and cyclophosphamide. Dose adjustments below starting dose level (level 1) apply to cyclophosphamide only.

Non-haematological toxicity - discuss with consultant:

Etoposide:

Renal impairment	**Hepatic impairment**
CrCl 15-50 mL/min: 75% dose CrCl < 15 mL/min: 50% dose Subsequent doses should be based on clinical response.	Consider: Bilirubin 26-51 micromol/L or AST 60-180 u/L 50% dose Bilirubin > 51 micromol/L or AST >180 u/L -clinical decision

Cyclophosphamide:

Renal impairment	**Hepatic impairment**
Clinical decision - consider whether patient is being treated with high dose. CrCl >20 mL/min: 100% dose CrCl 10-20 mL/min: 75% dose CrCl < 10 mL/min: 50% dose	Clinical decision. Exposure to active metabolites may not be increased, suggesting dose reduction may not be necessary.

Doxorubicin:

Renal impairment	**Hepatic impairment - clinical decision**
Discuss with consultant if renal impairment severe	Bilirubin 20-50 micromol/L 50% dose Bilirubin 51-85 micromol/L 25% dose Bilirubin > 85 micromol/L omit AST 2-3 x ULN 75% dose AST > 3 x ULN 50% dose

Doxorubicin maximum cumulative dose (additive to other anthracyclines):
450-550 mg/m^2 (in normal cardiac function)
400 mg/m^2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation)
but purpose of infusional doxorubicin is to reduce peak dose cardiac toxicity.

Vincristine:

Renal impairment	Hepatic impairment - clinical decision
No dose reduction	Bilirubin 26-51 micromol/L or ALT/AST 60-180 u/L 50% dose Bilirubin > 51 micromol/L & normal ALT/AST 50% dose Bilirubin > 51 micromol/L & ALT/ AST > 180 u/L omit

In the presence of motor weakness or severe sensory symptoms, discuss reducing or withholding vincristine with a consultant.

- Reduce dose 25% if grade 2 motor neuropathy develops
- Reduce dose 50% if grade 3 motor or sensory neuropathy develops
- Increase back to full dose if toxic effect for which the reduction was introduced lessens

INVESTIGATIONS

FBC, renal and liver profiles, only FBC result essential prior to administration of chemotherapy.

CONCURRENT MEDICATION

Allopurinol	300 mg daily for 7 days starting 24-48 hours prior to chemotherapy (first course / cycle only)
PPI (proton pump inhibitor)	Daily for the duration of steroid treatment in regimen
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
Co-trimoxazole	480 mg OD on Mondays, Wednesdays and Fridays each week.
Fluconazole	50 mg OD for duration of chemotherapy
G-CSF	from day 6 and continue until ANC > 5x 10^9/L- Supply 10 days treatment
Mesna (in patients with high dose cyclophosphamide or pre-existing bladder disorders)	The oral dose of mesna is 40% of the intravenous bolus dose of cyclophosphamide given on 3 occasions at intervals of 4 hours beginning 2 hours before the Cyclophosphamide injection; thus a total dose of mesna equivalent to 120% of cyclophosphamide is given. In patients at high-risk of urothelial toxicity, a shorter interval may be left between oral mesna doses, or the number of doses increased, or both. Alternatively, the initial dose of mesna (20% of the dose of cyclophosphamide) may be given intravenously at the same time as the antineoplastic drug, followed by two oral doses (each 40% of the dose of cyclophosphamide) given 2 and 6 hours after the intravenous dose.
Laxatives	Consider docusate 100-200 mg TDS PO and senna 1-2 tablets up to BD PO, patient to tailor dose.

ANTI-EMETICS

Days 1-5: Moderate
Day 5: High risk if cyclophosphamide on day 5 > 1500 mg/m^2

EXTRAVASATION RISK

Doxorubicin- Vesicant
Vincristine- Vesicant
Etoposide- Irritant
Cyclophosphamide- Neutral
Rituximab-Neutral

TREATMENT RELATED MORTALITY

1 – 2%

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