DOSE ADJUSTED EPOCH-R

INDICATION: Diffuse large B-cell lymphoma, Burkitt's lymphoma

The design of this regimen recognises the reduced resistance of lymphoma cells when exposed to continuous low concentrations of some cytotoxic agents when compared to brief high concentrations achieved with bolus doses. In addition it addresses the findings of pharmacokinetic studies showing significant interpatient variations in steady state dose concentrations. Doses are adjusted to achieve nadir neutrophils concentrations < 0.5 x 10^9/l. Patients at risk of CNS disease will receive additional intrathecal chemotherapy.

Prior to a course of treatment:

- Assess cardiac function by history & exam, ECG and CXR. If there is evidence of cardiac disease or risk factors, prior anthracyclines or patient > 70yrs perform a MUGA scan. If LVEF< 50% *discuss with consultant*
- Check FBC. Patient must have adequate marrow reserve – neutrophils >1.0, platelets >75 unless cytopaenia is due to disease, e.g marrow infiltration, splenomegaly
- Check renal and liver function – *discuss with consultant if abnormal*
- Consider intrathecal prophylaxis - *discuss with consultant*
- If appropriate discuss possibility of pregnancy with female patients and need for contraception with both male and female patients. Discuss risk of infertility – offer semen cryopreservation to male patients
- Ensure Hickman line in situ
- Written consent for course

Prior to each cycle:

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- Check FBC – neutrophils should be >1.0 and platelets >100 *(see dose modifications)*
- Check renal and liver function – *discuss with consultant if abnormal*

Rituximab	375mg/m^2	IV	Day 1 *(see protocol for rituximab)*
Infusional agents – Dose level 1 (see dose adjustments below)			
Doxorubicin	10mg/m^2/day	Continuous IV infusion	Days 1,2 3, 4 (96 hrs)
Etoposide	50mg/m^2/day	Continuous IV infusion	Days 1,2 3, 4 (96 hrs)
Vincristine	0.4mg/m^2/day *	Continuous IV infusion	Days 1,2 3, 4 (96 hrs)
Bolus agents			
Cyclophosphamide	750mg/m^2	IV	Day 5
Prednisolone	60mg/m^2	PO	Days 1-5

GCSF from day 6 to be continued through the nadir until neutrophils > 0.5 x 10^9/l

* vincristine dose is not to be capped

Cycle to be repeated every 21 days for up to 8 cycles

Dose adjustment levels according to nadir neutrophils and platelet counts
(based on twice-weekly FBCs taken 3 days apart eg. mon/thurs, tues/fri)

Nadir level	Dose adjustment
Nadir neuts at least 0.5 x 10^9/l	Increase dose of etoposide, doxorubicin and cyclophosphamide to 20% above dose given in last cycle.
Nadir < 0.5 x 10^9/l in at least 2 measurements	Same doses as last cycle
Nadir < 0.5 x 10^9/l in at least 3 measurements	Decrease dose of cyclophosphamide to 20% below dose given in last cycle.
Nadir platelet count < 25 x 10^9/l on at least one measurement	Decrease dose of etoposide, doxorubicin and cyclophosphamide to 20% below dose given in last cycle regardless of the nadir neutrophils count.

Dose adjustment for vincristine

Grade 2 **motor** neuropathy	Reduce dose by 25%
Grade 3 **motor** neuropathy	Reduce dose by 50%
Grade 3 **sensory** neuropathy	Reduce dose by 50%

If there is resolution of the toxic effect for which dose reduction was made escalate the does of vincristine to full dose again. Other side effects such as constipation should be managed aggressively without routine dose reduction.

Dose adjustments to above the starting (level 1) doses apply to doxorubicin, etoposide and cyclophosphamide.

Dose adjustments to below the starting (level 1) apply to cyclophosphamide only.

Prophylaxis for acute emesis	5HT antagonist
Prophylaxis for delayed emesis	5HT antagonist + metaclopramide 3-4 days
Other medications	Allopurinol 300mg od days 1-5 for cycle 1
	Cotrimoxazole 480mg od throughout

Written by	Dr MP Macheta, Consultant Haematologist
Date	25th October 2011