R-ICE (based on the CORAL TRIAL)

INDICATION: Relapsed and refractory diffuse large B-cell lymphoma

Prior to a course of treatment

- Do not use R-ICE if there is urinary tract obstruction
- Check creatinine clearance and LFTs (*see dose modification)*
- Patient should have adequate bone marrow reserve before commencing treatment, i.e neuts >1.0, platelets >100, unless due to marrow infiltration, splenomegaly - *if not 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
- Written consent for course

Prior to each cycle:

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- FBC – neutrophils must be > 1.0, platelets >50 *(see dose modification)*
- U&Es, creat, LFTs & creatinine clearance (*see dose modification)*
- If PBSC harvest planned inform transfusion lab that further blood products must be irradiated beginning from 7 days prior to harvest until completion.
- Assess venous access or arrange for insertion of femoral line following cycle 2/3 with a view to apheresis

Day –2	Rituximab	375mg/m^2 in 0.5L N saline	IV *(see protocol for rituximab)*
NOTE: Rituximab is given on day –2 with cycle 1 only			
Day 1	Etoposide	100mg/m^2 in 1.0L N saline#	IV over 1 hour
	Rituximab	375mg/m^2 in 0.5L N saline	IV *(see protocol for rituximab)*
Day 2	Etoposide	100mg/m^2 in 1.0L N saline#	IV over hour
	Carboplatin	in 0.5L 5% dextrose *(see a, b))*	IV over 1 hour
	<u>Ifosfamide and mesna</u>		
T - 5mins	Mesna 1g/m^2 IV in 100ml normal saline		
T = 0 hrs	Ifosfamide 5g/m^2 IV + mesna 5g/m^2 combined in 3.0L normal saline over 24 hours		
	(i.e 3 x 1.0L bags with 1/3 total doses each given over 8 hrs)		
T + 28 hrs	Mesna 1g/m^2 IV in 100ml normal saline		
T + 32 hrs	Mesna 1g/m^2 IV in 100ml normal saline		
T + 36 hrs	Mesna 1g/m^2 IV in 100ml normal saline		
Day 3	Etoposide	100mg/m^2 in 1.0L N saline#	IV over 1 hour
From day 6	GCSF	5mcg/kg SC daily *	continue until neutrophils have passed through the nadir and are > 0.5

If etoposide < 200mg give in 0.5L, if >200mg give in 1.0L

* If *PBSCH planned after cycle 3 use GCSF10mcg/kg from day 6 and continue until harvesting completed*

Repeat cycle every 21 days for 2 - 6 cycles

a. Dosed to an area under the curve of 5, according to the Calvert formula (*5 x [creatinine clearance + 25] , the maximum dose of carboplatin is 800mg corresponding to a creatinine clearance of 135ml/min)*

b. Before administering carboplatin check urine output is >100ml/hr - if output is 60-100ml/hr give 20% mannitol 200ml over 30mins

c. Ifosfamide may cause haemorrhagic cystitis, therefore concurrent administration of mesna is essential and adequate urine output must be maintained. Urinalysis must be performed every 4-6 hours - if there is microscopic haematuria increase the diuresis and consider further mesna 1g IV bolus. If there is frank haematuria stop ifosfamide and *discuss with consultant* - consider mesna 3g/m^2 in 2-3L N saline over 12 hours

Prophylaxis for acute emesis	5HT antagonist + dexamethasone
Prophylaxis for delayed emesis	Dexamethasone + 5HT antagonist for 3-4 days
Other medications	Allopurinol 300mg od for 5 days for cycle 1
	Anti-infective prophylaxis according to local policy

Dose modification for haematological toxicity

- There are no dose reductions in subsequent cycles but neutrophils must be > 1.0 and platelets >50 prior to each cycle – if treatment is delayed by ≥ 2 weeks further treatment may be inappropriate - *discuss with consultant*

Dose modification for neurological toxicity

- If there is grade 1 neurological toxicity (confusion, disorientation, attention deficit, somnolence or sedation not interfering with function), reduce dose of Ifosfamide to 3g/m^2 for the next cycle.
- If there is ≥ 2 neurological toxicity (as for grade 1 and interfering with function or activities of daily living), or toxicity increases despite dose reduction, Ifosfamide should be stopped.

Dose modification for renal dysfunction

- Increased risk of encephalopathy with ifosfamide when renal function is impaired

	Ifosfamide	Etoposide
• Creatinine clearance > 60ml/min	100% dose	100% dose
• Creatinine clearance 40 – 60ml/min	70% dose	100% dose
• Creatinine clearance < 40ml/min	Clinical decision	80% dose

Dose modification for liver dysfunction (unless due to disease)

- Dose adjustment generally suggested e.g 50% dose ifosfamide if ALT/AST > 2.5 x upper limit of normal, but there is limited information – clinical decision

Treatment of Central Nervous Toxicity of Ifosfamide

- Symptoms include lethargy, confusion, disorientation, mood changes, tonic-clonic spasms, motor unrest, emotional lability and altered conscious level. If these occur ifosfamide should be stopped and the case discussed with the consultant.
- Methylene blue is reported to be effective in reversing 'ifosfamide encephalopathy'. 1-2mg/kg is given IV over several minutes (1% solution) and may be repeated after one hour if required. Note it is contraindicated in severe renal failure and, if extravasation occurs or it is given subcutaneously, necrotic abscesses may result - the extravasation policy should be followed.

R-ICE Toxicities

Neutropenic sepsis	Mucositis
Thrombocytopenia	Amenorrhoea & infertility (offer semen cryopreservation)
Nausea& vomiting (moderate)	Ifosfamide encephalopathy – in ~10% patients (*see below)*
Alopecia	Nephrotoxicity
Ototoxicity	Haemorrhagic cystitis
Fever, chills, hypotension, rigors & anaphylaxis (rituximab) – usually first dose only	Hypotension, chest pain, dyspnoea, flushing and bronchospasm (etoposide)

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