FRACTIONATED OUTPATIENT (R)-ICE

Indication: Relapsed and refractory lymphoma

Prior to a course of treatment

- Do not use R-ICE if there is urinary tract obstruction
- Check FBC, U&Es, creatinine, calculated GFR and LFTs (*see dose modification)*
- Check hepatitis B and C serology
- 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
- Neuts must be > 1.0, platelets >50, check U&Es, creat, LFTs & calculated GFR (*see dose modification)*
- Patient must be instructed to observe for haematuria with each void. They must contact the Haematology Unit immediately if they notice blood in the urine or become drowsy (see c.)
- If PBSC harvest planned inform transfusion lab that further blood products must be irradiated beginning from 7 days prior to harvest until completion. Liaise with transplant CNS to ensure results of virology are known and NBS is aware of planned PBSC mobilisation. Note NBS demand the virology results checked in their own laboratories and may refuse to process the harvest if the results are not known.
- Assess venous access or arrange for insertion of femoral line following cycle 2/3 with a view to apheresis

Day 1	Ifosfamide	1667mg/m^2 in 1.0L N saline	IV over 2 hrs
	Mesna	1667mg/m^2 in 1.0 L N saline	
	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	Ifosfamide	1667mg/m^2 in 1.0L N saline	IV over 2 hrs
	Mesna	1667mg/m^2 in 1.0 L N saline	
	Etoposide	100mg/m^2 in 1.0L N saline$^{\#}$	IV over 1 hour
	Carboplatin	in 0.5L 5% dextrose *(see a, b)*	IV over 1 hour
Day 3	Etoposide	100mg/m^2 in 1.0L N saline$^{\#}$	IV over 1 hour
	Ifosfamide	1667mg/m^2 in 1.0L N saline	IV over 2 hrs

	Mesna	1667mg/m^2 in 1.0 L N saline
From day 6	GCSF	GCSF 5mcg/kg (if *PBSCH planned after cycle 3 use GCSF10mcg/kg*)

Repeat cycle every 21 days for 2 - 6 cycles

Rituximab may be given on day - 1 or day – 2

If stem cell harvest is planned start counting peripheral blood CD34 count when WBC >1.0 x 10^9/L

Mesna

- Ifosfamide is given together with mesna 1667mg/m^2 made up together in 1 litre N saline (total dose is 5g/m^2).
- Oral mesna 2000mg PO at 2hrs and 6 hrs after completion of ifosfamide infusion (take 6hr dose at home). Patient must contact the Haematology Unit if they are vomiting or unable to take the mesna.
- Instruct patient to maintain oral fluid intake of >2L for next 24 hours

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. If there is frank haematuria during the infusion stop ifosfamide and increase the diuresis. The patient must be admitted for continued hydration and observation. Consider mesna 3g/m^2 in 2-3L N saline over 12 hour

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 or consider prophylactic methylthioninium chloride (methylene blue.)
- 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 or prophylaxis, Ifosfamide should be stopped.

Dose modification for renal dysfunction

- Note 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.
- Methylthioninium chloride (Methylene blue) is reported to be effective in reversing 'ifosfamide encephalopathy'. 1-2mg/kg is given IV over several minutes (0.5% solution/5mg/ml) 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 above)*
Alopecia	Nephrotoxicity
Ototoxicity	Haemorrhagic cystitis
Fever, chills, hypotension, rigors & anaphylaxis (rituximab) – usually first dose only	Hypotension, chest pain, dyspnoea, flushing and bronchospasm (etoposide)
Stevens-Johnson syndrome (rituximab)	Cytokine-release syndrome (rituximab, potentially fatal)

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Date:	10th August 2016
	10th August 2019