R-CODOX-M FOR PATIENTS < 65 YEARS (R-CODOX-M/IVAC TRIAL)

Indications: Burkitt's lymphoma, high grade B-cell lymphoma

Prior to treatment

- Consider fitness for treatment carefully – R-CODOX-M is a very intensive chemotherapy regimen. For fulminant cases initial treatment with full or attenuated dose CHOP may be appropriate.
- Assess cardiac function by history & exam, ECG and CXR. If there is evidence of cardiac disease or risk factors or prior anthracyclines perform a MUGA scan. If LVEF< 50% R-CODOX-M may be inappropriate – *discuss with consultant*
- Check hepatitis B & C serology
- Check FBC, U&Es, creat, calcium, phosphate, urate, coagulation screen – abnormalities at diagnosis are usually due to disease
- 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.
- Ensure Hickman line is in situ
- Written consent for course

Prophylaxis for acute tumour lysis syndrome

- If there is acute renal failure at presentation investigate urgently for possible urinary tract obstruction – this should be relieved by ureteric stenting or nephrostomies. Dialysis may be indicated.
- Review the use of potentially nephrotoxic drugs, e.g NSAIDs, and avoid potassium supplements or potassium-sparing diuretics (including ACE inhibitors), and uricosuric agents, e.g thiazides, probenecid, which may promote crystallisation.
- Give Rasburicase 0.2mg/kg in 50ml normal saline IV over 30mins daily. *Review Rasburicase daily with consultant.* Allopurinol is unnecessary.
- Hydrate with 4.5L/m^2 per 24hrs aiming for at least 3.0L/m^2 per 24hrs. Aim for a diuresis of at least 150ml/hr - give IV frusemide if necessary to maintain diuresis and maintain fluid balance.
- Give 75mmol/l sodium - equivalent to ½ normal saline-5% dextrose. Do not add KCl unless K < 3.0mmol/l.
- When Rasburicase is used urinary alkalinisation is unnecessary.
- Monitor fluid balance carefully
- Check FBC, coagulation, U&Es, creat, calcium, phosphate at least daily. If there is more severe electrolyte disturbance more frequent monitoring may be indicated

Prior to each cycle

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- It is important to maintain treatment intensity for Burkitt's lymphoma – commence 2nd and later cycles on the first day unsupported neutrophils > 1.0, platelets > 75
- Check U&Es, creat, LFTs – see dose modifications in trial protocol

Prior to high dose methotrexate

- Read protocol for high dose methotrexate
- Stop drugs with potential to interact with methotrexate e.g cotrimoxazole, NSAIDs, and review use of nephrotoxic drugs
- Check creatinine clearance by 24hr urine as close to the methotrexate as possible – see dose modifications
- If creatinine clearance has been normal with a previous cycle creatinine clearance only needs to be repeated if serum creatinine has increased by at least 20% of the previous value or if there has been an intervening reason for impairment of renal function.

- Only give methotrexate if serum creatinine is normal and creatinine clearance is >50ml/min/$m^{2.}$
- Methotrexate is given on day 10 irrespective of the FBC.
- The duration of the methotrexate infusion must not exceed 24hrs regardless of the dose given.
- Alkalinise the urine by giving 3.0L/m^2 /24hrs IV fluid with bicarbonate to maintain urine pH >7.0 prior to and during methotrexate infusion. Start 18-24 hrs before methotrexate and continue alkalinisation until folinic acid rescue has been completed. Prescribe sodium bicarbonate 3g PRN also.
- Check U&Es, creat daily during methotrexate
- Check methotrexate levels 48hrs after starting methotrexate infusion, then daily until methotrexate level < 5.0 x 10^{-8}M.
- Start folinic acid 15mg/m^2 at 36hrs after start of methotrexate infusion. This can be given orally after the first 24hrs if the patient is compliant and not vomiting. Dose of folinic acid may be increased depending on methotrexate level – *see high dose methotrexate protocol*.

Day 1	Cyclophosphamide		800mg/m^2	IV bolus	
	Vincristine		1.5mg/m^2 in 50ml Nsaline (max. 2mg)	IV over 5mins	
	Doxorubicin		40mg/m^2	IV bolus	
	Rituximab		375mg/m^2 in 500ml Nsaline	IV	See protocol for rituximab
Day 2	Cyclophosphamide		200mg/m^2	IV bolus	
	Cytarabine		70mg	IT	
Day 3	Cyclophosphamide		200mg/m^2	IV bolus	
Day 4	Cyclophosphamide		200mg/m^2	IV bolus	
	Cytarabine		70mg	IT	
Day 5	Cyclophosphamide		200mg/m^2	IV bolus	
Day 8	Vincristine		1.5mg/m^2 in 50ml Nsaline (max. 2mg)	IV over 5mins	
Day 10	T = 0hr	Methotrexate	300mg/m^2	IV in 100ml N saline over 1hr	
	T + 1 hr	Methotrexate	2700mg/m^2	IV in 1.0L N saline over 23 hrs	
	Pre and post hydration as per protocol for high dose methotrexate. Methotrexate infusion must stop at T +24hrs				
	T + 36hrs	Folinic acid	15mg/m^2	IV	
	T = 36-48hr	Folinic acid	15mg/m^2	IV every 3 hrs	
	T + 48hr	Folinic acid	15mg/m^2	* IV 6hrly until MTX <5 x10^{-8} M (23ng/ml)	
	** Can be given orally after first 24hrs if not vomiting. Comes as 15mg and 30mg tablets*				
Day 11	Rituximab		375mg/m^2 in 500ml Nsaline	IV	
Day 13	Neulasta		6mg s.c		

Day 15	Methotrexate	12mg	IT

Intensified intrathecal chemotherapy for patients with proven or suspected CNS disease at presentation

The following schedule is given with the first cycle of R-CODOX-M:

Day 2, 4, 6 Cytarabine 70mg IT

Day 15, 17 Methotrexate 12mg

For cycle 3 intrathecal therapy is given according to the schedule for patients without CNS disease

Prophylaxis for emesis	Day 1 -2:	5-HT antagonist + dexamethasone
	Days 3 - 5:	5-HT antagonist
	Day 10:	5-HT antagonist+ metoclopramide

R-CODOX-M Toxicities

Acute tumour lysis syndrome	Neutropenic sepsis & thrombocytopaenia
Nausea and vomiting	Mucositis
Alopecia	Autonomic neuropathy (constipation, ileus)
Sensory and motor neuropathy	Haemorrhagic cystitis
Amenorrhoea, infertility (offer semen cryopreservation)	Nephrotoxicity
Diarrhoea, gastrointestinal ulceration and bleeding	Hepatotoxicity (acute transaminitis)
Acute pulmonary toxicity (fever, cough, interstitial infiltrates)	Rash
Cardiomyopathy	Jaw pain
Fever, rigors, hypotension, anaphylaxis (rituximab)	

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