FLUDARABINE, CYCLOPHOSPHAMIDE & RITUXIMAB

INDICATION: CLL

Prior to a course of treatment

- Check calculated creatinine clearance - *see dose modification*
- Check FBC. Patient should have adequate bone marrow reserve, i.e neutrophils > 1.0, platelets >75 unless cytopaenia is due to disease, e.g marrow infiltration, splenomegaly
- If lymphs >25 x 10^9/l or there is bulky disease e.g lymph node mass > 10cm, patients are at risk of a potentially fatal cytokine release syndrome with the first infusion of rituximab. This infusion must therefore be given with close monitoring and observation, and the dose of rituximab should be split over 2 days (see below).
- 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 males
- Inform transfusion lab that irradiated blood products will be required
- Check hepatitis B and C serology
- 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 >75 *(see dose modification)*
- Check calculated creatinine clearance – consider gradual dose escalation according to renal function and haematological toxicity in earlier cycles

Day 1	Rituximab	375mg/m^2 (cycle 1) 500mg/m^2 (cycles 2-6)	IV in 0.5L N saline

There is a risk of tumour lysis syndrome with rituximab when there is a lymphocytosis hence use with caution and monitor closely when lymphs > 25 x 10^9/l. Consider splitting rituximab over 2 days with first cycle giving 50mg/m^2 on day 1 and 325mg/m^2 on day 2 with cycle 1

Refer to template for administration of rituximab
Rituximab must not be given by rapid infusion schedule

Day 1-5	Fludarabine	24mg/m^2	PO
Day 1-5	Cyclophosphamide	150mg/m^2	PO

Cyclophosphamide tablets should be taken at breakfast and fludarabine tablets at lunchtime

Note fludarabine is supplied as 10mg tablets, cyclophosphamide as 50mg tablets so round doses up or down as required

Nausea & diarrhoea are common with oral fludarabine – an intravenous regimen given over 3 days may be better tolerated

Day 1-3	Fludarabine	25mg/m^2 in 100ml Nsaline	IV over 30mins
Day 1-3	Cyclophosphamide	250mg/m^2	IV bolus

Cyclophosphamide should be injected immediately before fludarabine for optimum effect

Repeat cycle every 28 days for up to 6 cycles

Premedication	Paracetamol 1g PO, chlorphenamine 10mg IV.
Prophylaxis for acute emesis	5HT antagonist for 5 days
Prophylaxis for delayed emesis	5HT antagonist + metoclopramide for 3-4 days *(do not use dexamethasone for antiemetic prophylaxis)*
Other medications	Allopurinol 300mg od (100mg od if Cr Cl <20ml/min) for 7 days with cycle 1
	Cotrimoxazole 480mg od until 6 months after completion
	Acyclovir 400mg bd

Dose modifications haematological toxicity (unless due to disease)

• Day 28 neuts <1.0 or plats <75	Delay treatment for up to 2 weeks & reduce dose of cyclo/fludara by 25% for subsequent cycles if counts recover
• Neuts 0.5-1.0 or plats 50-75 despite two weeks delay	Proceed with chemotherapy at 50-75% dose
• Day 28 neuts 0.5-1.0 or plats 50-75 despite 25% dose reduction	Reduce to 50% original doses of cyclo/fludara
• Day 28 neuts <0.5 or plats <50	Delay until theses levels reached then proceed as above

Growth factor support with GCSF may be appropriate in some cases - discuss with consultant

Dose modification for renal dysfunction

• Creatinine clearance 30-60ml/min	50% fludarabine
• Creatinine clearance <10ml/min	Stop fludarabine

Cytokine-release syndrome

- This is a potentially fatal complication of rituximab therapy which is more common when there are circulating malignant lymphocytes.
- It usually occurs 1 -2 hours of starting the first infusion and is characterized by severe dyspnoea, often with bronchospasm, hypoxia plus tachycardia, hypotension, fever, chills, rigors, urticaria and angioedema. A pulmonary infiltrate may be seen on CXR and respiratory failure may develop.
- There may be features of tumour lysis syndrome such as hyperuricaemia, hypocalcaemia, acute renal failure and a raised LDH.
- Thrombocytopenia, liver dysfunction and DIC may also occur.
- If this occurs stop infusion and inform consultant. Monitor patient closely and perform FBC, U&Es, creat, LFTs, Calcium, phosphate, coagulation and CXR, plus ABGs if hypoxic.
- After resolution of all symptoms and signs further treatment with rituximab can be considered. Further treatment has rarely resulted in a repeat of the cytokine release syndrome. Infusion should be resumed at no more than half the initial rate.

Fludarabine, cyclophosphamide & rituximab toxicities	
Neutropenic sepsis	Nausea (moderate-severe)
Thrombocytopenia	Alopecia
Auto-immune haemolysis	Amenorrhoea & infertility (offer semen cryopreservation)
Opportunist infections	Hepatotoxicity
Diarrhoea	Encephalopathy – coma, cortical blindness (rarely)
Fever, chills, rigors, hypotension, bronchospasm, anaphylaxis with rituximab	Rash, Stevens-Johnson syndrome
Delayed neutropenia	Progressive multifocal leucoencephalopathy
Pulmonary fibrosis	Cytokine release syndrome
Reactivation of hepatitis B and C infection	

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