VRCAP

INDICATION: Previously untreated mantle cell lymphoma

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 hepatitis B & C serology
- Check renal and liver function – *see dose modification and discuss with consultant if abnormal*
- 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
- Check FBC & U&Es - neutrophils should be >1.5 and platelets > 75 unless due to lymphoma *(see dose modifications) Discuss with Consultant*

Rituximab	375mg/m^2 in 0.5L N saline	IV	day 1 *(see protocol for rituximab)*
Cyclophosphamide	750mg/m^2	IV bolus	day 1
Doxorubicin	50mg/m^2	IV bolus	day 1
Bortezomib	1.3mg/m^2	subcutaneous	Days 1, 4, 8, 11 (allow at least 72 hours between doses)
Prednisolone	100mg/m^2	PO	days 1-5
Cycle to be repeated every 21 days for up to 8 cycles			

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

Dose modification for neutropenia (unless due to lymphoma) and infection

• Neutrophils < 1.0 on day 1	Delay 1 week and proceed at 100% if they recover
• Neutrophils remain < 1.0 despite delay	Give GCSF for up to 1 week
• If no recovery despite GCSF	Further treatment may be inappropriate - *discuss with consultant*
• If treatment is delayed > 1week, or >1 delay, or an episode of neutropenic sepsis	GCSF prophylaxis with subsequent cycles

• If further treatment delay or neutropenic sepsis despite GCSF	Consider proceeding at 50-75% dose cyclophosphamide & doxorubicin – *discuss with consultant*
Dose modification for thrombocytopenia (unless due to lymphoma)	
• Platelets <75 on day 1	Delay cycle 1-2 weeks – if no recovery consider proceeding at 50-75% dose cyclophosphamide & doxorubicin or proceed at 100% dose with platelet support if needed - *discuss with consultant*
• Platelets < 25 on days 4, 8 or 11	Consider platelet support if count <25 to avoid delay or omit bortezomib (discuss options with consultant)
For cardiotoxicity	
• If symptoms or signs of cardiac failure develop, discontinue doxorubicin and measure LVEF by MUGA scan. *Inform consultant*.	
• Consider substituting doxorubicin with etoposide (see 'modified CHOP-like' protocol) – *discuss with consultant*	
For liver dysfunction (unless due to lymphoma)	
• Bilirubin <1.5x upper limit of normal	100% dose doxorubicin
• Bilirubin 1.5 – 3 x upper limit of normal	50% dose doxorubicin. Reduce bortezomib to 0.7mg/m^2 for 1st cycle and adjust dose (to 0.5mg/m^2 or 1mg/m^2) for subsequent cycles based on tolerability
• Bilirubin > 3 x upper limit of normal	Consider 25% dose of cyclophosphamide and doxorubicin. Adjust bortezomib dose as above
For renal dysfunction	
• If Creat. Clearance <10ml/min	Consider stopping cyclophosphamide and doxorubicin or using 50% cyclophosphamide. Consider reducing bortezomib -*discuss with consultant*
For bortezomib neurological toxicity	
• Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)	Reduce bortezomib to 1mg/m^2 or change schedule to 1.3mg/m^2 weekly
• Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL)	Withhold bortezomib until symptoms have resolved. Restart at 0.7mg/m^2 per week
• Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue bortezomib

Toxicities

Neutropenic sepsis	Mucositis
Thrombocytopenia	Sensory & motor neuropathy
Nausea & vomiting (moderate)	Autonomic neuropathy (constipation, ileus)
Alopecia	Amenorrhoea & infertility (offer semen cryopreservation)
Cardiomyopathy	Jaw pain
Hyperglycaemia	Haemorrhagic cystitis

Fever, hypotension, rigors, anaphylaxis (rituximab)

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Reference

N Engl J Med. 2015 Mar 5;372(10):944-53. doi: 10.1056/NEJMoa1412096