BORTEZOMIB - MELPHALAN - PREDNISOLONE (VMP) for patients with NEWLY DIAGNOSED myeloma NOT eligible for PBSCT **OFF TRIAL**

INDICATION: Newly diagnosed myeloma in older or less fit patients not eligible for PBSCT (NICE technology appraisal TA228 July 2011 approved use in patients where thalidomide was contraindicated or not tolerated but then wording extended to all patients in the base-line commissioning update 2013)

Prior to a course of treatment

- Assess cardiac function by history and exam with ECG, CXR. Consider MUGA scan if abnormal. Note bortezomib is contraindicated if severe cardiac impairment.
- Assess for peripheral neuropathy – may worsen on therapy; contraindicated if * Grade 3 sensory
- Check FBC, U&Es, LFTs – *see dose modification - discuss with consultant if there is renal impairment*
- In the absence of prior cytotoxic therapy cytopenias probably reflect marrow infiltration therefore give at least first cycle at full dose.
- Written consent for course
- Encourage patient to drink 3 L fluid daily

Prior to each cycle

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- Check FBC – neutrophils must be > 1.0, platelets > 75 - *see dose modification*
- Encourage patient to drink 3L fluid daily

Bortezomib (Velcade®)	1.3mg/m^2	s/c on days **1,4,8,11,** then **22,25,29,32 (**see below**)**
Melphalan*	9mg/m^2	OD orally days 1 to 4 inclusive
Prednisolone	60mg/m^2	OD orally days 1 to 4 inclusive

Repeat cycle every 42 days (i.e. 1 cycle = 6 weeks) for maximum of 4 cycles depending on tolerance and response before switching to weekly bortezomib (can use weekly bortezomib from beginning if so wish**):**

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Melphalan*	9mg/m2	OD orally days 1 to 4 inclusive
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(*comes as 2mg tablets)

Anti-emetic prophylaxis	Metoclopramide
Other medications	Allopurinol 300mg od (100mg if Cr.Cl <20ml/min) for cycle 1 Prophylactic acyclovir 400mg bd recommended

Bortezomib dose modifications:

Dose modification for neutropenia (unless due to disease)

• Neutrophils <0.5 or platelets <25 on day 1 of cycle	Stop until > 1.0 then restart at 1.0 mg/m^2 if initially 1.3mg/m^2 or 0.7 mg/m^2 if initially 1.0mg/m^2 **OR** GCSF prophylaxis
• No resolution of neutropenia or recurs at 0.7mg/m^2	Consider stopping treatment – *discuss with consultant*

Dose modification for thrombocytopenia (unless due to disease)

• Platelets <25 on day 1 of cycle	Stop until >25 then restart at 1.0 mg/m^2 if initially 1.3mg/m^2 or 0.7 mg/m^2 if initially 1.0mg/m^2 **OR** Support with platelet transfusion
• No resolution of thrombocytopenia or recurs at 0.7mg/m^2	Consider stopping treatment – *discuss with consultant*

Dose modifications for peripheral neuropathy

• Grade 1 (but no pain) i.e loss of tendon reflexes or paraesthesiae but not interfering with function	Reduce to 1.3mg/m^2 weekly
• Grade 1 with pain or Grade 2, i.e objective sensory loss or paraesthesia interfering with function but not activities of daily living	Reduce to 1.0mg/m^2 weekly
• Grade 2 with pain or Grade 3, i.e sensory loss or paraesthesia interfering with activities of daily living	Withhold until symptoms resolve, then restart at 0.7mg/m^2 weekly. If symptoms fail to resolve within 2 weeks – stop treatment
• Grade 4, i.e permanent sensory loss that interferes with function	Discontinue bortezomib

Modification for renal dysfunction

- If < 30ml/min *discuss with consultant*. Note that the incidence of serious adverse effects increases with mild-moderate renal impairment. Patients have been treated safely when the creatinine clearance is<30ml/min and on dialysis but monitor carefully for toxicities if renal function is impaired.

Modification for liver dysfunction

- The major route of bortezomib excretion is hepatic and there is limited on the use of bortezomib in patients with hepatic impairment. If bilirubin >30μmol/L use with caution, monitor closely for toxicity and consider dose reduction – *discuss with consultant*

Dose modification for diarrhoea

• If ≥ grade 3 diarrhoea, i.e increase of ≥ 7 stools/day over baseline, incontinence, hospitalization with >24 hrs IV fluids	Reduce dose to 1.0mg/m^2, then 0.7mg/m^2 if symptoms persist

Bortezomib Toxicities

Thrombocytopenia	Nausea
Neutropenic sepsis	Fatigue
Fluid retention & cardiac failure	Diarrhoea, constipation & ileus
Peripheral neuropathy (may be painful)	Hypotension
Fatigue, malaise, weakness	

Melphalan dose modifications

Dose modifications for haematological toxicity (unless considered due to marrow infiltration)

- If neutrophils <1.0 and/or platelets <75 — Delay treatment for up to 2 weeks
- If there is treatment delay > 2 weeks due to neutropenia on > 1 occasion — Consider GCSF for 2-3 days per cycle

Dose modifications for renal insufficiency

- If creatinine > 200μmol/L despite rigorous hydration initially reduce dose of melphalan to 5mg/m^2
- Then consider titrating dose according to haematological toxicity

Melphalan Toxicities	
Neutropenic sepsis & thrombocytopaenia	Nausea (none-mild)
Alopecia (uncommon)	Amenorrhoea & infertility (offer semen cryopreservation)
Mucositis	Rash
Second malignancies (late)	Pulmonary fibrosis (late)

Prednisolone dose modification

If prednisolone poorly tolerated reduce dose to 30mg/m^2. If still poorly tolerated consider weekly dosing.

No dose modification needed in renal failure

Prednisolone Toxicities

Agitation, confusion, depression	Insomnia
Oedema, fluid retention	Peptic ulceration
Proximal myopathy	

References:

- VISTA (Velcade as Initial Standard Therapy in Myeloma) trial Investigators. Bortezomib plus melphalan and prednisolone for initial treatment of multiple myeloma. San Miguel et al. N Engl J Med, 2008;359(9): 906 – 917
- GEM 2005 Trial Update comparing VMP/VTP as induction in elderly multiple myeloma patients: do we still need alkylators? Mateos et al, September 18, 2014; Blood: 124 (12)

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