Myeloma SVd protocol

Selinexor (nexpovio®) + bortezomib (velcade®) + dexamethasone

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INDICATION: myeloma patients who have had one previous line of treatment only and are refractory to both daratumumab and lenalidomide. In the NHS at the time of writing this only applies to transplant-ineligible patients relapsing through first-line daratumumab + lenalidomide + dexamethasone.

Prior to consent

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function.
- Check FBC, U&Es and LFTs, hepatitis and HIV screen. Discuss with consultant if significant cytopenia or if renal or hepatic function have changed significantly.

Selinexor	**100 mg**	oral weekly on day 1, 8,15, 22 & 29 (should not exceed 70mg/m^2 per dose)
Velcade® (bortezomib)	**1.3 mg/m^2**	s/c weekly day 1, 8, 15 & 22
Dexamethasone (for patients over age 75 consider weekly dex on same day as selinexor)	**20 mg**	oral twice-weekly on days 1 & 2, 8 & 9, 15 & 16, 22 & 23, 29 & 30 **1 cycle = 35 days. Continue until disease progression or unacceptable toxicity**

Pre-medications	Allopurinol 300mg od for 7 days (100mg if Cr.Cl <20ml/min) for cycle 1 only, acyclovir 400mg BD cotrimoxazole 480mg daily prophylaxis throughout antiemetic prophylaxis with ondansetron 8mg 1 hour prior to Selinexor and TDS dosing for 2 days post dose. If nausea persists, add metoclopramide 10mg TDS. Also consider adding olanzapine 2.5 – 5mg nocte for 2 nights after Selinexor. Loperamide should be used as required for diarrhoea

Selinexor Toxicities

Selinexor is a first-in-class selective inhibitor of nuclear export by inhibition of exportin-1 (XPO1) which is over-expressed in myeloma cells, leading to accumulation of tumour-suppressor proteins, reduction in oncoproteins and apoptosis of the malignant plasma cells.

Nausea	Vomiting	Diarrhoea	Anorexia & weight loss
Thrombocytopenia	Neutropenia	Fatigue	Hyponatraemia

Selinexor dose modification

Selinexor comes as 20mg tablets so dose reductions for toxicity would be to reduce from 100mg weekly to 80mg, then to 60mg if further toxicity, then 40mg if toxicity remains and then discontinue if toxicity still present. For cytopenias and diarrhoea consider reducing selinexor before reducing bortezomib.

No dose modification is required for renal failure

No studies or recommendation available for hepatic failure

Bortezomib Toxicities

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

Bortezomib dose modification

Dose modification for thrombocytopenia (unless due to disease)

• Platelets <25 on day 1 of cycle **(remember to reduce selinexor first)**	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	No change
• 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
• 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 at once a week. 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 creatinine clearance < 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*

Table 6: Recommended starting dose modification for bortezomib in patients with hepatic impairment

Grade of hepatic impairment*	***Bilirubin level***	***SGOT (AST) levels***	***Modification of starting dose***
Mild	*≤ 1.0 x ULN*	*> ULN*	*None*
	> 1.0 x-1.5x ULN	*Any*	*None*
Moderate	*> 1.5 x-3x ULN*	*Any*	*Reduce bortezomib to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.*
Severe	*> 3 x ULN*	*Any*	

Abbreviations: SGOT=serum glutamic oxaloacetic transaminase; AST=aspartate aminotransferase; ULN=upper limit of the normal range.

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 but **consider selinexor dose reductions first**

Appendix 1:

International Myeloma Working Group Criteria for progressive disease requires an increase of ≥ 25% from the lowest response value in any one or more of the following:

1. Serum M-component (the absolute increase must be ≥ 5 g/L)
2. Urine M-component (the absolute increase must be ≥ 200 mg/24hrs)
3. Involved serum free light chain level increase of ≥ 200mg/L in 2 consecutive measurements separated by ≤ 2 months (plus an abnormal FLC ratio)
4. Bone marrow plasma cell percentage (the absolute percentage must be ≥ 10%)
5. Development of new soft tissue plasmacytoma or bone lesions
6. Hypercalcaemia > 2.65 mmol/L

International Myeloma Working Group Criteria for relapse requires one or more of the following:

1. Development of new soft tissue plasmacytoma or bone lesions
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
3. Hypercalcaemia > 2.65 mmol/L
4. Decrease in Hb of ≥ 20 g/L
5. Rise in serum creatinine to ≥ 177 mmol/L
6. Hyperviscosity

References:

- Once-per-week Selinexor, bortezomib and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomized, open-label, phase 3 trial. Grosicki et al, The Lancet, Nov 14, 2020, vol 396, issue 10262 p1563-1573.

- Consensus Recommendations for the uniform reporting of clinical trials: report of the international myeloma workshop consensus panel 1. Rajkumar et al, Blood, May 5, 2011, vol 117, No18, p 4691–4695.

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