Modified CyBorD/ Bortezomib, cycloPHOSphamide and dexAMETHasone –Weekly Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of newly diagnosed symptomatic multiple myeloma	C90	00299a	Hospital
Treatment of relapsed/refractory multiple myeloma	C90	00299b	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Bortezomib, cycloPHOSphamide and dexAMETHasone are administered weekly for four weeks on days 1, 8, 15 and 22 in a 28 day treatment cycle for four treatment cycles or until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Cycle
1,8,15,22	Bortezomib	[a]1.5mg/m^2	[b,c] SC (abdomen or thigh)	Every 28 days
1,8,15,22	cycloPHOSphamide	[d]300mg/m^2	PO	Every 28 days
1,8,15,22	dexAMETHasone	40mg	PO Take in the morning with food	Every 28 days
[a]A dose of 1.3mg/m^2 may be more suitable in certain patients at the discretion of the prescribing consultant				
[b]Note: Bortezomib may be administered as IV bolus over 3-5 seconds through a peripheral or central intravenous catheter followed by a flush with 0.9% NaCl. Note the concentration of bortezomib solution should be 1mg/ml when administered via the IV route.				
[c]The solution should be injected subcutaneously, at a 45-90^0 angle. Injection sites should be rotated for successive injections. If local injection site reactions occur, either a less concentrated solution may be administered sc or a switch to intravenous injection is recommended. At least 72 hours should elapse between consecutive doses of bortezomib. Bortezomib is a proteasome inhibitor and is neurotoxic. **Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer**. *Here*				
[d]cycloPHOSphamide is available as 50mg tablets. They should be swallowed with sufficient fluid without chewing. The tablets should not be divided before use.				

ELIGIBILITY:

- Indications as above
- ECOG 0-2

- Patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment.

EXCLUSIONS:

- Hypersensitivity to bortezomib, boron, cycloPHOSphamide or any of the excipients
- Acute diffuse infiltrative pulmonary and pericardial disease

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal, liver and bone profile
- Uric acid
- Clotting screen
- Blood pressure, *Blood glucose if being treated with oral hypoglycaemics (*See Drug Interactions).
- Assessment of peripheral neuropathy status.
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), C and HIV
  ***See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation**

Regular tests:

- FBC; monitor platelet count **at a minimum** of day 1 and prior to day 15 of each cycle
- Renal, liver and bone profile prior to each cycle.
- Blood pressure
- *Blood glucose if being treated with oral hypoglycaemics. (* See Drug Interactions)

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

Table 1: Dose reduction steps for bortezomib

Dose Level	Dose
Starting dose	1.5mg/m^2
Dose level 1	1.3mg/m^2
Dose level 2	1.0mg/m^2
Dose level 3	0.7mg/m^2

Haematological:

Table 2: Dose modifications for bortezomib and cycloPHOSphamide for haematological toxicity

Haematological Toxicity	Dose Modification
Grade 3	
• First occurrence	Omit cycloPHOSphamide on day 22 only Reduce bortezomib dose by one level (from 1.5 mg/m^2 to 1.3mg/m^2 **or** from 1.3mg/m^2 to 1mg/m^2)
• Second occurrence	Omit cycloPHOSphamide on day 15 and day 22 Reduce bortezomib from 1.3 mg/m^2 to 1mg/m^2 **or** from 1mg/m^2 to 0.7mg/m^2)
• Third occurrence	Omit cycloPHOSphamide on day 8 and day 15 and day 22 Reduce bortezomib to 0.7mg/m^2
Grade 4 (ANC < 0.5 x10^9/L) • First occurrence	Withhold treatment until symptoms of the toxicity have resolved. Treatment may be re-initiated at a 25% reduced dose (1.3mg/m^2 reduced to 1.0mg.m^2; 1.0mg/m^2 reduced to 0.7mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.

Renal and Hepatic Impairment:

Table 3: Recommended dose modifications renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th>Grade of Hepatic Impairment*</th><th>Bilirubin Level</th><th>SGOT (AST) levels</th><th>Modification of starting dose</th></tr>
<tr><td rowspan="5">Bortezomib</td><td colspan="2" rowspan="5">It is unknown if the pharmacokinetics of bortezomib are influenced in patients with severe renal impairment not undergoing dialysis (CrCL < 20ml/min). Since dialysis may reduce bortezomib concentrations, it should be administered after the dialysis procedure</td><td rowspan="2">Mild</td><td>≤1 x ULN</td><td>> ULN</td><td>None</td></tr>
<tr><td>>1 - 1.5 x ULN</td><td>Any</td><td>None</td></tr>
<tr><td>Moderate</td><td>>1.5 - 3 x ULN</td><td>Any</td><td rowspan="3">Reduce dose to 0.7mg/m^2 in the first treatment cycle. Consider dose escalation to 1mg/m^2 or further dose reduction to 0.5mg/m^2 in subsequent cycles based on patient tolerability.</td></tr>
<tr><td>Severe</td><td>> 3 x ULN</td><td>Any</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td rowspan="4">cycloPHOSphamide</td><td>CrCl (ml/min)</td><td>Dose</td><td colspan="4" rowspan="4">Severe impairment : Clinical decision</td></tr>
<tr><td>>20</td><td>100%</td></tr>
<tr><td>10-20</td><td>75%</td></tr>
<tr><td><10</td><td>50%</td></tr>
</table>

*****Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).

Neuropathic pain and/or peripheral neuropathy:

Table 4: Dose modifications for bortezomib related neuropathy

Severity of neuropathy	Dose Modification
Grade 1	None
Grade 1 with pain or Grade 2	Reduce dose to 1mg/m^2
Grade 2 with pain or Grade 3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment and reduce dose to 0.7mg/m^2 once every week
Grade 4 and/or severe autonomic neuropathy	Discontinue treatment
Grade 1: Asymptomatic; clinical or diagnostic observations only Grade 2: Moderate symptoms; limiting instrumental Activities of Daily Living (ADL) Grade 3: Severe symptoms; limiting self-care ADL Grade 4: Life-threatening consequences; urgent intervention indicated *Grading based on NCI Common Toxicity Criteria CTCAE v 4*	

Dose reductions for other toxicities:

Table 5: Dose modification schedule based on adverse events

Adverse reactions*	Recommended dose modification
Grade ≥3 Non-haematological toxicity	Withhold treatment until symptoms of the toxicity have resolved. Treatment may be re-initiated at a 25% reduced dose (1.3mg/m^2 reduced to 1.0mg.m^2; 1.0mg/m^2 reduced to 0.7mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.
Cystitis Grade 1 or 2 • First occurrence • Second occurrence • Third occurrence Grade 3 or 4 • 1st occurrence	 Omit cycloPHOSphamide on day 22 only Omit cycloPHOSphamide on day 15 and 22 only Omit cycloPHOSphamide on day 8, day 15 and day 22 Consider discontinuation of cycloPHOSphamide
New or worsening pulmonary symptoms (e.g. cough, dyspnoea)	Withhold treatment. Prompt diagnostic evaluation required and benefit/risk ratio should be considered prior to continuing bortezomib therapy.
Posterior Reversible Encephalopathy Syndrome (PRES)	Discontinue bortezomib.

*Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

SUPPORTIVE CARE

EMETOGENIC POTENTIAL:
cycloPHOSphamide – Moderate **(Refer to local policy).**
Bortezomib- Low **(Refer to local policy).**

PREMEDICATIONS: Not usually required. Ensure patient remains well hydrated during treatment.

OTHER SUPPORTIVE CARE:

- Bisphosphonates should be considered in all patients with myeloma related bone disease. **(Refer to local policy).**
- Consider the use of a H_2 antagonist or proton pump inhibitor if appropriate in patients receiving dexAMETHasone therapy **(Refer to local policy).**
- Tumour Lysis Syndrome prophylaxis **(Refer to local policy).**
- Antiviral prophylaxis **(Refer to local policy).**
- Consider PJP prophylaxis **(Refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. **(Refer to local infectious disease policy)**. These patients should be considered for assessment by hepatology.

Bortezomib

- **Peripheral Neuropathy:** Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.
- **Hypotension**: Treatment is commonly associated with orthostatic/postural hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting.
- **Hepatic Impairment;** Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with bortezomib at reduced doses and closely monitored for toxicities.
- **Haematological toxicity:** Gastrointestinal and intracerebral haemorrhage have been reported in association with bortezomib treatment. Therefore platelet counts should be monitored prior to each dose of bortezomib and bortezomib should be withheld when the platelet count is < 25x 10^9cells/L. Potential benefit of treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding. Complete blood counts with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. Platelet transfusion should be considered when clinically appropriate.
- **Progressive multifocal leukoencephalopathy (PML):** Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PM is suspected patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue bortezomib if PML is diagnosed.
- **Gastrointestinal toxicity:** Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with bortezomib treatment.
- **Seizures:** Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.
- **Posterior Reversible Encephalopathy Syndrome (PRES):** In patients developing PRES, treatment with bortezomib should be discontinued.
- **Heart Failure**: Acute development or exacerbation of congestive heart failure, and/or new onset of

decreased left ventricular ejection fraction has been reported during bortezomib treatment. Patients with risk factors for or existing heart disease should be closely monitored.
- **Renal Impairment:** Patients with renal impairment should be monitored closely.

cycloPHOSphamide:
- **Haemorrhagic cystitis (HC):** HC has been associated with low dose cycloPHOSphamide therapy.

dexAMETHasone:
- **Steroid use:** Steroid use is associated with numerous side effects including insomnia, gastric irritation, increased blood sugar levels, mood changes, increased appetite, bruising, skin fragility and osteoporosis (long term use).

DRUG INTERACTIONS:
- Additive hypotensive effect with antihypertensives. Blood pressure should be monitored and ensure patient is well hydrated prior to bortezomib dose. Adjustment of antihypertensives may be required.
- During clinical trials, hypoglycaemia and hyperglycemia were uncommonly and commonly reported in diabetic patients receiving oral hypoglycaemics. Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.
- Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates.
- CYP3A inhibitors also decrease the conversion of cycloPHOSphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- CYP3A inducers increase the conversion of cycloPHOSphamide to both its active and inactive metabolites.
- cycloPHOSphamide inhibits cholinesterase metabolism of suxamethonium which may prolong its neuromuscular blocking effect.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	08/08/2016		Dr John Quinn
2	12/10/2018	Updated with new NCCP regimen template. Standardisation of dose modifications for cyclophosphamide in renal impairment. Updated dose modifications for skin rash and inclusion of adverse effects of bortezomib	Dr John Quinn
3	08/03/2021	Regimen review Addition of table for dose reduction steps for bortezomib Updated dose modification recommendation for cyclophosphamide in renal impairment Updated adverse events/regimen specific complications with regard to PML, gastrointestinal toxicity and management of hepatitis B reactivation..	Dr John Quinn

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed regimen for the use of Bortezomib® in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy