

BORTEZOMIB BEST PRACTICE

A guide for nurses

Developed by the Myeloma Special Practice Network (M-SPN) of the Haematology Society of Australia and New Zealand (HSANZ) Nurses Group



FOREWORD

Haematology Society of Australia and New Zealand Nurses' Group (HSANZ-NG) is a sub-group within the HSANZ that represents the interest of its nurse members. Their mission is to enhance the care of patients undergoing treatment for haematological conditions, and support their relatives and caregivers, through the development and promotion of information and education aimed at improving the standards of care. The Myeloma Special Practice Network (M-SPN) was specifically formed to focus on enhancing care of those affected by myeloma.

The M-SPN identified a major practical issue for nurses in the management of multiple myeloma (MM) patients was the lack of a standardised best practice guidelines on the administration of bortezomib. Therefore, the group set out to develop this guide for nurse to provide an overview of the current best practice recommendations regarding the administration, management of toxicities, use of assessment tools, and provide resources to help standardise nursing practice in Australia.

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INTRODUCTION

The proteasome inhibitor bortezomib (Velcade®), alone and in combination, is highly effective in the treatment of patients with MM, producing high response rates and resulting in improved overall survival across disease settings.¹⁻³ Grade ≥ 3 adverse events (AEs) reported in $\geq 10\%$ of patients in phase III clinical studies of single-agent intravenous (IV) bortezomib include peripheral neuropathy (PN), thrombocytopenia, neutropenia, and anaemia.⁴⁻⁶ Nurses play a crucial role in the management of patients on treatment, and are responsible for the follow-up and monitoring, so are best placed to manage adverse reactions. Their role includes direct patient care, identifying and addressing clinical problems, and maximising effective treatment outcomes. Therefore, it is important that nurses are aware of the potential side-effects of treatment and recognise these symptoms early, so adverse reactions can be effectively managed and minimised by dose modification or concomitant therapy.

Bortezomib was initially only approved for administration via the IV route, however, subcutaneous (SC) administration was found to have non-inferior efficacy in terms of overall response rate.^{4,7} SC bortezomib also resulted in fewer grade ≥ 3 AEs than the IV route (57% vs 70%), less PN of any grade (38% vs 53%, $p=0.044$), and fewer dose reductions, due to adverse events (31% vs 43%).⁴ Currently, there is a lack of clear direction in the literature in terms of the optimal injection technique for the administration of bortezomib.⁸ This can pose a challenge in terms of ensuring consistency in how bortezomib is administered in practice. Inconsistent injection techniques can result in patients experiencing injection site reactions (ISR) and pain, whereas use of optimal technique may reduce the risk of AEs.^{9,10}

Educating nurses about the optimal administration of bortezomib and management of AEs may help to improve patient outcomes, by emphasising the importance of consistent caring and evidence-based practice. Adopting a best practice protocol for bortezomib administration has the potential to reduce incidence and severity of ISRs, whilst ensuring the effective and safe delivery of the drug. This will facilitate treatment continuation and efficacy, reduced incidence of AEs and limited time spent by patients in the clinical setting.

This bortezomib best practice document for nurses is intended to:

- Provide consensus on best practice in delivery of bortezomib to patients with MM
- Reduce the variance in bortezomib administration practice nationally
- Provide additional patient information resources to support optimal education.

DOSING

I. Reconstitution

A vial of bortezomib can be used for either SC or IV administration. However, it is important to note that the reconstituted concentration of SC bortezomib is different from the IV formulation. The preparation will be reconstituted by your hospital pharmacist according to the bortezomib Approved Product Information,¹¹ reconstitution instructions depending on whether it is to be administered by SC or IV route. This ensures bortezomib is reconstituted under aseptic conditions. Refer to the bortezomib PI for further information.¹¹

II. Delivery schedules

The administration route and schedule of bortezomib may vary between treatment centres. While bortezomib can be administered via IV or SC injection, the more common route is SC and therefore this document will focus on safe administration of bortezomib via the SC route.

A non-inferiority, phase III, randomised, open-label trial compared the efficacy and safety of bortezomib SC administration (n=148) with IV administration (n=74) in patients with relapsed MM.^{4,11} Patients who did not obtain a complete response (CR) after 4 cycles were allowed oral dexamethasone. The primary endpoint was overall response rate (ORR) at 4 cycles. Secondary endpoints included response rate at 8 cycles, median time to progression (TTP) and progression-free survival (PFS), 1-year overall survival, and safety.⁴ After a median follow-up of 11.8 months in the SC group and 12.0 months in the IV group, there were no significant differences in TTP (median 10.4 months, 95% CI 8.5–11.7, vs 9.4 months, 7.6–10.6; p=0.387) and 1-year overall survival (72.6%, 95% CI 63.1–80.0, vs 76.7%, 64.1–85.4; p=0.504) with SC versus IV bortezomib. Grade ≥ 3 AEs were reported in 57% of patients in the SC group versus 70% in the IV group; the most common were thrombocytopenia (13% vs 19%), neutropenia (18% vs 18%), and anaemia (12% vs 8%). PN of any grade (38% vs 53%; p=0.044), grade ≥ 2 (24% vs 41%; p=0.012), and grade ≥ 3 (6% vs 16%; p=0.026) was significantly less common with SC than with IV administration. SC bortezomib offers non-inferior efficacy to standard IV administration, with an improved safety profile.

A typical starting dose of bortezomib is 1.3 mg/m². Dose modifications are applied in the presence of toxicity or frailty, at the discretion of the treating clinician. The length of treatment will differ between those who are eligible for stem cell transplant (SCT) compared with those who are ineligible for SCT. Different schedules may be used for patients who are receiving treatment for newly-diagnosed disease, compared with those who are receiving treatment for relapsed disease, as well as patients who are receiving bortezomib in combination with other drugs.¹¹

A weekly schedule of bortezomib is often used when patients experience toxicity or are considered frail, as this dosing schedule has been shown to be more tolerable and resulted in a similar cumulative dose delivered compared to the traditional schedule of bortezomib on days 1,4,8,11 every 21 days.^{14,15} However, this dosing schedule is not consistent with the recommended dosing in the bortezomib Australian Approved Product Information.¹¹

Table 1: Commonly used induction bortezomib-based regimens for upfront treatment of newly diagnosed MM patients, prior to autologous stem cell transplantation (ASCT).¹²

Regimen	Schedule
CyBorD/BCD	Bortezomib: 1.3 mg/m ² IV (or SC) D1,4,8,11; Cyclophosphamide: 300 mg/m ² po D1,8,15,22 (or cyclophosphamide 900 mg/m ² IV D1); Dexamethasone: 20 mg po on day of and day after bortezomib OR Bortezomib: 1.5 mg/m ² IV (or SC) D1,8,15,22; Cyclophosphamide: 300 mg/m ² po D1,8,15,22; Dexamethasone: 20 mg po on day of and day after bortezomib. Cycles repeated every 28 days x for 3–4 cycles prior to ASCT
BD	Bortezomib: 1.3 mg/m ² IV (or SC) D1,4,8,11; Dexamethasone: 20 mg on day of and day after bortezomib. Cycles repeated every 21 days for 3-4 cycles prior to ASCT
PAD	Bortezomib: 1.3 mg/m ² IV (or SC) D1,4,8,11; Doxorubicin: 20/m ² IV D1 and 4 OR Doxorubicin: 9 mg/m ² IV D1,2,3,4 (daily bolus or continuous infusion); Dexamethasone: 20 mg po daily, D1,2,4,5,8,9,11,12. Cycles repeated every 3 weeks for 3-4 cycles prior to ASCT

D: Day; po: by mouth.

Table 2: Commonly used initial induction bortezomib-based regimens for upfront treatment of newly diagnosed MM patients, who are not eligible for ASCT.¹³

Regimen	Schedule
BMP	Bortezomib: 1.3 mg/m ² IV (SC preferable) D1, 4, 8, 11, 22, 25, 29, and 32 (cycles one to four) and days 1, 8, 22, and 29 (cycles five to nine) every 6 weeks for nine cycles; Melphalan: 9 mg/m ² orally D1-4 every 6 weeks for nine cycles; Prednisone: 60 mg/m ² orally D 1-4 every 6 weeks for nine cycles
BCD	Bortezomib: 1.5 mg/m ² IV (SC preferable) D1,8,15,22 every 4 weeks for 4 to 12 cycles; Cyclophosphamide: 300 mg/m ² orally D1,8,15,22, every 4 weeks for 4 to 12 cycles; Dexamethasone: 40 mg orally D1,8,15,22 every 4 weeks for 4 to 12 cycles
Bd	Bortezomib: 1.3 mg/m ² IV (SC preferable) D1,4,8, and 11 IV every 3 weeks for six cycles; Dexamethasone: 40 mg orally on day of and day post-bortezomib

III. Dosing modifications

Dose modification and re-initiation of bortezomib may be necessary due to AEs during treatment. Bortezomib therapy should be withheld at the onset of any grade 3 non-haematological or grade 4 haematological toxicities, excluding neuropathy.¹¹ Once the symptoms of the toxicity have resolved, treatment may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1.0 mg/m²/dose; 1.0 mg/m²/dose reduced to 0.7 mg/m²/dose).¹¹

Severe autonomic neuropathy, resulting in treatment interruption or discontinuation, has been reported. Patients with pre-existing severe neuropathy, should be treated with bortezomib only after careful risk/benefit assessment.¹¹

Prior to initiating a new cycle of bortezomib treatment, it is important to check to confirm the patients:¹¹

- Platelet count is $\geq 70 \times 10^9/L$
- Absolute neutrophil count (ANC) is $\geq 1.0 \times 10^9/L$
- Non-haematological toxicities have resolved to grade I or baseline.

Table 3: Dose management guidelines for bortezomib.¹¹

Haematological toxicity	Dose modification or delay
If platelet count is $\leq 30 \times 10^9/L$ or ANC is $\leq 0.75 \times 10^9/L$ on bortezomib dosing day (other than Day 1)	Bortezomib dose should be withheld
If several bortezomib doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	Bortezomib doses should be reduced by 1 dose level (from 1.3 mg/m ² , or from 1 mg/m ² to 0.7 mg/m ²)
Grade ≥ 3 non-haematological toxicities	Bortezomib therapy should be withheld until symptoms of the toxicity have resolved to grade I or baseline. Then, bortezomib may be reinitiated with one dose level reduction (from 1.3 mg/m ² to 1 mg/m ² , or from 1 mg/m ² to 0.7 mg/m ²) For bortezomib-related neuropathic pain and/or PN, hold and/or modify bortezomib.

Patients with hepatic impairment do not require a starting dose adjustment and should be treated as per the recommended bortezomib dosing.¹¹ Patients with moderate and severe hepatic impairment should be treated with caution at reduced starting doses of bortezomib (0.7 mg/m² per injection) and closely monitored for toxicities.¹¹

Table 4: Recommended starting dose modifications for bortezomib in patients with hepatic impairment.¹¹

	Bilirubin level	SGOT (AST) levels	Modification of starting dose
Mild	≤1.0 x ULN	>ULN	None
	>1.0 x – 1.5 x ULN	Any	None
Moderate	>1.5 x – 3.0 x ULN	Any	Reduce bortezomib to 0.7 mg/m ² in the first cycle.
Severe	>3.0 x ULN	Any	Consider dose escalation to 1.0 mg/m ² or further dose reduction to 0.5 mg/m ² in subsequent cycle based on patient tolerability

AST: Aspartate aminotransferase; SGOT: Serum glutamic oxaloacetic transaminase; ULN: Upper limit of the normal range.

IV. Blood monitoring surveillance

Due to the potential for myelosuppression, it is crucial to ensure patients have satisfactory neutrophil and platelet count recovery before proceeding with bortezomib treatment.¹¹ Be mindful that each institution will follow their own blood monitoring surveillance policy, and this document is specific to blood monitoring for bortezomib treatment, separate consideration must be made for blood monitoring requirements for combined therapies and patient specific comorbidities.

Recommendations for blood monitoring surveillance

It is recommended prior to the commencement of therapy to check the full blood count (FBC) weekly for the first cycle.¹¹

If the platelet count remains >50 x10⁹/L for the whole cycle and if on Day 1 of Cycle 2, neutrophils are >1.5 x10⁹/L, and platelets >100 x10⁹/L, monthly FBC monitoring prior to each cycle is sufficient for the duration of subsequent treatment cycles, unless the clinical scenario changes.¹⁶

ADMINISTRATION

To be effective in demonstrating a consistent pharmacokinetic profile, medications administered via the SC route must be delivered into the adipose tissue. The recommendations detailed here are based on the administration of SC bortezomib as stated by Kurtin et al., 2012, and the International Myeloma Foundation Nurse Leadership Board.^{17,18} These recommendations were proposed to ensure the safe and effective delivery of bortezomib into adipose tissue, not the muscle, based on site selection, use of appropriate injection site technique, and needle length.

Skin irritation can occur as a side effect of SC administration. It is important to try to minimise the risk of ISRs, so patient's physical and psychological well-being is not impacted. Severe ISRs can lead to higher rates of dose reduction and/or discontinuation. There are four steps you should follow to ensure adequate drug absorption, while minimising the risk of skin irritation (see *Recommendations for SC injection administration*).

Bortezomib is an irritant and so it is important to change needles after drawing up the medication and prior to injection, to avoid leaving an injection track.¹⁷ Studies have shown that SC injections of 30 seconds, or 10-seconds followed by a 10-second delay before withdrawing the needle, result in significantly less bruising and pain compared with 10-second injections alone.^{19,20}

I. Recommendations for SC injection administration

Step 1: Choose an appropriate injection site

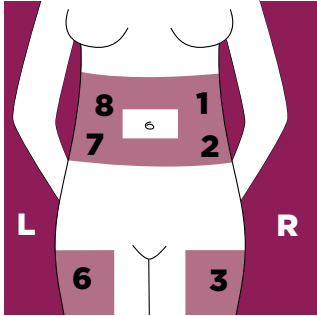
- Inject into an injection site with adequate adipose tissue (pinch an inch using index finger and thumb, avoid pinching the muscle).
- Avoid the 2 cm region around the umbilicus.
- Rotate injection sites each time and use the following recommended sites: abdomen, upper outer aspects of the thighs (see figure 1).
- Never inject into skin which is tender, bruised, erythematous, or indurated, and always document the injection site, so this area is not used for the next injection.
- Injection sites should be a minimum of 1 cm apart.

AVOID:

- Areas prone to friction, i.e. belt-line, seatbelt region
- Injecting into hair follicles
- Areas with scarring, birthmarks, inflammation, and impaired skin integrity.

NOTE: *There is no pharmacokinetic data available to support administration of bortezomib into the arm, therefore we do not recommend using this site.²¹*

Figure 1: Bortezomib SC injection site rotation.



Within the same cycle

- Injections at same site were avoided.
- Alternated between
 - right and left abdomen
 - upper and lower quadrant or between right and left thigh
 - proximal and distal sites.

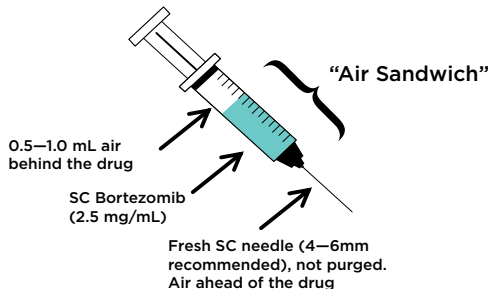
Step 2: Use air sandwich technique

Use of this technique can help avoid seeding of irritating medication in the injection track and ensure maximum delivery into the SC tissue (see figure 2).

NOTE: This technique should NOT be used for IV injections.

- Attach a fresh 26 gauge needle (4–6 mm) to the syringe
- Do NOT purge the air in the needle
- Maximum volume for an SC injection is 2 mL per site
- Pull 0.5–1.0 mL of air into the syringe to create an air pocket behind the drug when the needle is inverted
- Using the index finger and thumb pinch an inch of skin at the selected injection site
- Invert the syringe contents, including the air behind the drug.

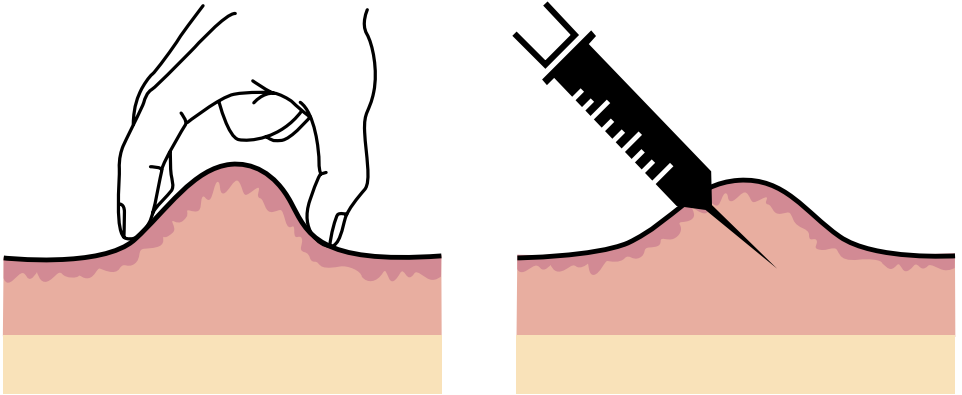
Figure 2: Air sandwich technique



Step 3: Use correct administration angle and needle choice

- Use a 90° angle for a needle length of 4–6 mm, 26 gauge needle is appropriate.
- If the needle length is ≥ 8 mm, or the patient has minimal adipose tissue, then a 45° angle will ensure administration into the subcutaneous tissue, not muscle (see figure 3).

Figure 3: Skin lift technique



Step 4: Inject slowly

- Inject the contents of the needle over a 30 second period, or 10 seconds followed by a 10-second delay, before withdrawing the needle.
- Remove the needle after injecting and apply gentle pressure to the injection site.

II. Managing an Injection Site Reaction

ISRs have been reported in clinical trials and post-marketing experience with chemotherapeutic agents, administered via the SC route.^{22,23} ISRs are associated with discomfort, patient body image concerns due to visible skin changes, and emotional distress. Bortezomib ISRs are relatively common, however, these are usually mild (grade 1/2).^{4,17,24}

The most common presentation is erythema or hyperpigmentation of a 2–3 cm area surrounding the injection site, which may be accompanied by pruritus (see figure 4). This usually resolves in days to weeks, the reported median time to symptom resolution is 6 days.^{17,25} More severe reactions have been reported in clinical practice, including areas of hyperpigmentation exceeding 10 cm, variable degrees of induration, and in some cases scab formation at the injection site.

Recommendations state that the treatment for ISRs may include the administration of oral antihistamines.¹⁷ Topical application of cool compress, antihistamines, or corticosteroids is not recommended within 4 hours of administration, to avoid changes in pharmacokinetics. It is important to provide patients with education about post-injection care, including details of aggravating factors to avoid and how to manage symptoms associated with ISRs.

Figure 4: Example of a site reaction after SC injection of bortezomib (Image provided courtesy of Myeloma Australia).



In order to assess the severity of the ISR, it is important to grade the severity of the reaction. The National Cancer Institute (NCI) provide guidance on the Common Terminology Criteria for Adverse Events (CTCAE).²⁶

Table 5: Grading of ISRs according to the NCI-CTCAE.²⁶

Adverse event	1	2	3	4	5
ISR	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain, lipodystrophy, edema, phlebitis	Ulceration or necrosis, severe tissue damage, operative intervention indicated	Life-threatening consequences, urgent intervention indicated	Death

Definition of ISR: A disorder characterised by an intense adverse reaction (usually immunologic) developing at the site of an injection.

Recommendations for managing ISRs:

- Review the patient history, including medication profile, other injectable medications, antiplatelet/anticoagulation medications, and thrombocytopenia.
- Provide advice to patients on how to self-manage any ISRs, including the following information:
 - Avoid massaging or friction around the injection site (wear loose-fitting clothing, avoid rubbing the site immediately after injection).
 - Apply warm or cool compress to relieve discomfort. Patients should be advised NOT to apply these immediately after injection, or within 4 hours post-injection, as it may interfere with drug absorption and pharmacokinetics.
 - Topical application of corticosteroids, such as hydrocortisone, may be of benefit for pruritic symptoms, but should also not be used within 4 hours post-injection.

POTENTIAL SIDE EFFECTS OF BORTEZOMIB

Side effects experienced with bortezomib are varied, although the majority are readily manageable, with standard interventions and/or dose modification. Commonly reported AEs include, asthenic conditions, PN, haematologic events, and gastrointestinal problems (see table 6).^{6,11} Nurses should be aware of the spectrum of associated side effects to ensure they can monitor patients for ongoing safety. If measures are not put in place to ensure the early identification of complications this may impact on patient adherence, quality of life, and ultimately be life threatening.⁶

Table 6: Common AEs during treatment reported in 15% or more of patients, receiving bortezomib, including Grade 3 and Grade 4 events.⁶

Most commonly reported AEs (>15%) n=331	All (%)	Grade 3 (%)	Grade 4 (%)
≥1 event	100	61	14
Diarrhea	57	7	0
Nausea	57	2	0
Fatigue	42	5	<1
Constipation	42	2	0
PN	36	7	1
Vomiting	35	3	0
Pyrexia	35	2	0
Thrombocytopenia	35	26	4
Anaemia	26	9	1
Cough	21	1	0
Paresthesia	21	2	0
Dyspnea	20	5	<1
Neutropenia	19	12	2
Rash	18	1	0
Insomnia	18	<1	0
Abdominal pain	16	2	0
Bone pain	16	4	0
Pain in limb	15	2	0
Muscle cramps	12	0	0

I. Peripheral neuropathy

PN is characterised by tingling or numbness in the hands, arms, feet, or legs. This may occur because of bortezomib treatment, but it is important to be aware that PN may also be caused by protein deposits due to myeloma (10–20%), and is a common side effect with other MM treatments, including thalidomide and vincristine.²⁷ PN is the most troubling adverse event associated with bortezomib and can significantly impact patient well-being. It is important that monitoring occurs frequently and if it is detected the dose should be reduced, making it manageable. If symptoms are more severe, bortezomib may be stopped for a time until the symptoms improve and then restarted at a lower dose.

Recommendations for assessment of PN

- It is important to monitor patients' symptoms at baseline of treatment, prior to administering subsequent doses, and at the onset of worsening PN by questioning patients about their experience of PN and recording this information on a neurotoxicity assessment tool (see table 7 and appendix I).
- It is important to be aware of any pre-existing conditions involving neurological damage (i.e. diabetes) as this increases the risk of PN.

Recommendations for managing PN

The International Myeloma Working Group (IMWG) have developed evidence-based dose-modification guidelines for bortezomib (Available at: <http://imwg.myeloma.org/tag/peripheral-neuropathy/>).¹⁴ Early and prompt use of these guidelines has been shown to lead to improvement of resolution of PN while maintaining therapeutic efficacy.

A variety of over-the-counter preventative supplements have been proposed, including B-complex vitamins, glutamine, and folic acid, although support of their use is based mostly on anecdotal evidence.^{14,28} The use of any over-the-counter supplements should only be recommended in consultation with the treating clinician.

Table 7: Grading of PN based on NCI-CTAE.²⁶

Severity of PN signs and symptoms	Bortezomib dose
Grade 1 (paresthesias weakness, and/or loss of reflexes) without pain or loss of function	- Reduce current bortezomib dose by one level (1.3 to 0.7 mg/m ²) OR for patients receiving a twice-weekly schedule, change to a once-a-week schedule using the same dose - Consider starting with 1.3 mg/m ² once per week in patients with history of prior PN
Grade 1 with pain or Grade 2 with no pain but limiting instrumental activities of daily living	- For patients receiving twice-weekly bortezomib, reduce current dose by one level, or change to once-per-week schedule using the same dose - For patients receiving bortezomib on a once-per-week schedule: reduce current dose by one level, OR consider temporary discontinuation. Upon resolution (grade ≤1), restart once-per-week dosing at lower dose level in cases of favourable benefit-to-risk ratio
Grade 2 with pain or Grade 3 limiting self care and activities of daily living or Grade 4 disabling	Discontinue bortezomib

II. Thrombocytopenia

Thrombocytopenia is one of the most clinically significant side effects associated with bortezomib treatment. The development of thrombocytopenia can be dependent upon a patients' baseline platelet count and the degree of bone marrow plasma cell infiltration.²⁹

When isolated thrombocytopenia is present at the time of the next dose or cycle of bortezomib, doses are often withheld or modified in order to preserve bone marrow function, and lower the risk of long-term thrombocytopenia.³⁰

Recommendations for managing thrombocytopenia

- Due to an increased risk of bleeding with thrombocytopenia, for a platelet count of less than $<30 \times 10^9/L$ delay bortezomib dose and reinitiate at a reduced dose and provide platelet transfusion support if indicated.¹¹

III. Infection

Infection is a major cause of morbidity and mortality for MM patients. The increased susceptibility of patients to infection results from the interplay between antineoplastic therapies, age, and disease.³¹ Full blood examination should be done routinely to monitor for infection (Refer to blood monitoring surveillance in the administration section). Recommendations for the management of the risk of infection are based on the bortezomib PI and Myeloma Scientific & Advisory Group (MSAG) guidelines.^{11,32}

Recommendations for managing the risk of infection

- Educate patients about the signs and symptoms of infection and give examples of symptoms they may experience, including:
 - Temperature of $>38^{\circ}C$
 - Experiencing chills and sweats
 - Productive cough
 - Sore throat
 - Diarrhoea and vomiting
- Recommend patients receive an annual influenza vaccination to reduce their seasonal influenza risk.
- Live vaccinations are contraindicated in all patients with MM and/or on immunosuppressive therapy.
- In patients receiving bortezomib in combination with high-dose corticosteroids, recommend Bactrim therapy, to reduce the risk of pneumocystic jiroveci infections.
- Recommend patients are prescribed anti-viral prophylaxis to reduce the risk of varicella reactivation, this should be continued for the duration of bortezomib treatment, especially if in combination with dexamethasone.³² The type of anti-viral prescribed will depend on the hospital formulary, but may include: valaciclovir; acyclovir; or famciclovir.

IV. Gastrointestinal problems

Gastrointestinal problems (e.g., nausea, vomiting, diarrhoea, constipation) are the most common side effects of bortezomib treatment. Generally, if symptoms occur it will be during the first or second cycle, and are usually mild to moderate.³³ If not acted upon early, these side effects can have a deleterious effect on patient quality of life and interfere treatment adherence and outcomes.^{28,34}

Recommendations for managing gastrointestinal problems

- Provide patient education regarding strategies to avoid and treat gastrointestinal problems, including:
 - Importance of maintaining adequate hydration (>2 litres of fluid per day)
 - Use of anti-emetics (e.g., ondansetron and metoclopramide)
 - Eating a high fibre diet and aperients
 - Use of anti-diarrhoeal medication (e.g., loperamide) and dietary changes, such as the BRAT diet (bananas, rice, apple sauce, toast)^{28,35}
- Educate patients to seek advice if symptoms persist without relief for ≥ 2 –3 days.

V. Hypotension

Hypotension and dizziness are side effects of bortezomib associated with its effect on the autonomic nervous system.³⁶ Bortezomib should be used cautiously in patients with a history of syncope, receiving medications known to be associated with hypotension, those who are dehydrated.¹¹ Management of orthostatic/postural hypotension may include: adjustment of antihypertensive medications; increased hydration; increased salt intake; or the administration of corticosteroids with mineralocorticoid effects.

Recommendations for managing hypotension

- Ensure you regularly check the blood pressure prior to bortezomib treatment
- For patients with a history of low blood pressure, or who are taking anti-hypertensive medications, it is particularly important to proceed with caution. Notify the treating physician if you are concerned or a patient is symptomatic (i.e. experiencing dizziness).
- Patients should be encouraged to drink plenty of water on the days leading up to, and on the day of treatment to avoid dehydration and subsequent hypotension.

VI. Tumour lysis syndrome

Bortezomib is a cytotoxic agent and can rapidly kill malignant cells, thus while rare, the complications of tumour lysis syndrome (TLS) may occur. The patients at risk of TLS are those with high tumour burden prior to treatment.¹¹

Recommendations for TLS:

- Patients should be monitored closely and appropriate precautions taken.
- If the patient is considered at risk of TLS, prophylactic allopurinol may be prescribed and adequate hydration strongly recommended.³⁷

VII. Posterior reversible encephalopathy syndrome

There have been reports of posterior reversible encephalopathy syndrome (PRES) in MM patients receiving bortezomib. PRES is a rare, reversible, neurological disorder, which can present as seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances.

Recommendations for PRES:

- Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis.
- In patients with PRES, discontinue bortezomib. The safety of reinitiating therapy in patients previously experiencing PRES is not known.

VIII. Cardiac disorders

Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction (LVEF) has been reported, including reports in patients on bortezomib, with few or no risk factors for decreased LVEF.¹¹

Recommendations for patients with cardiac disorders:

- Patients with risk factors for, or an existing heart disease should be closely monitored.

IX. Pulmonary disorders

There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology, such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving bortezomib.¹¹

Recommendations for patient with pulmonary disorders:

- In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation should be performed and patients treated appropriately.

X. Combination/Supportive therapy

Adjunctive supportive care is very important in patients with MM, and includes measures to treat complications of the disease and to prevent morbidity associated with the disease and its treatment. MSAG provide specific guidance on the use of supportive therapy for MM patients receiving bortezomib.³² You should refer to the MSAG guidelines for recommendations as they are aligned with local protocols.

REFERENCES

1. Moreau P, Richardson PG, Cavo M, et al. *Blood* 2012;120(5):947–59.
2. San Miguel JF, Schlag R, Khuageva NK, et al. *Journal of Clinical Oncology* 2013;31(4):448–455.
3. Sonneveld P, Goldschmidt H, Rosiñol L, et al. *Journal of Clinical Oncology* 2013;31(26):3279–87.
4. Moreau P, Pylypenko H, Grosicki S, et al. *The Lancet Oncology* 2011;12(5):431–40.
5. Orlowski RZ, Nagler A, Sonneveld P, et al. *Journal of Clinical Oncology* 2007;25(25):3892–901.
6. Richardson PG, Sonneveld P, Schuster MVW, et al. *The New England Journal of Medicine* 2005;352(24):2487–98.
7. Arnulf B, Pylypenko H, Grosicki S, et al. *Haematologica* 2012;97(12):1925–28.
8. Annersten M and Willman A. *Worldviews on Evidence-based Nursing* 2005;2(3):122–30.
9. Girouard N and Theoret G. *Canadian Journal of Neuroscience Nursing* 2008;30(4):18–25.
10. McEwan L, Brown J, Poirier J, et al. *International Journal of MS Care* 2010;12:177–89.
11. Bortezomib Approved Product Information. Janssen-Cilag Pty Ltd. Date approved February 2006. Date of latest amendment December 2016.
12. Jagannath S, Durie BG, Wolf J, et al. *British Journal of Haematology* 2005;129(6):776–83.
13. Khan ML, Reeder CB, Kumar SK, et al. *British Journal of Haematology* 2012;156(3):326–33.
14. Richardson PG, Delforge M, Beksac M, et al. *Leukemia* 2012;26(4):595–608.
15. Bringhen S, Larocca A, Rossi D, et al. *Blood* 2010;116(23):4745–53.
16. Raibakgar PS, Richardson PG, Sonneveld P, et al. *Blood* (ASH meeting 2010);116:Abstract 1963.
17. Kurtin S, Knopp CS, and Milliron T. *Journal of the Advanced Practitioner in Oncology* 2012;3(6):406–10.
18. International Myeloma Foundation (IMF). (2012). Velcade Treatment Approaches: A Report of findings from the 2013 Nurse Leadership Board Roundtable Meeting. Available at: https://www.myeloma.org/sites/default/files/images/research/NLB/nlb_velcadesq_wp13.pdf.
19. Akpınar B and Celebioglu A. *International Journal of Nursing Studies* 2008;45(6):812–17.
20. Zaybak A and Khorshid L. *Journal of Clinical Nursing* 2008;17(3):378–85.
21. Martin J, Beegle N, Zhu Y, and Hanisch E. *Journal of Advanced Practitioner in Oncology* 2015;6(4):308–18.
22. Kurtin SE and Demakos EP. *Clinical Journal of Oncology Nursing* 2010;14(3):E29–44.
23. Murray C, Wereley A, Nixon S, et al. *Canadian Oncology Nursing Journal* 2012;22(4):222–34.
24. Lamm W, Drach-Schauer B, Eder S and Drach J. *Oncology* 2013;85(4):223–7.
25. Ng P, Incekol D, Lee, R, et al. *Journal of Oncology Pharmacy Practice* 2015;21(4):285–92.
26. National Cancer Institute (NCI) and National Institutes of Health (NIH). Common Terminology Criteria for Adverse Events (CTCAE). Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.
27. San Miguel J, Blade J, Boccadoro M, et al. *Oncologist* 2006;11(1):51–61.
28. Faiman, B., Doss, D., Colson, K., et al. *Clinical Journal of Oncology Nursing* 2017;21(5):19–36.
29. Field-Smith A, Morgan GJ and Davies FE. *Therapeutics and Clinical Risk Management* 2006;2(3):271–9.
30. Lonial S, Waller EK, Richardson PG, et al. *Blood* 2005;106(12):3777–84.
31. Nucci M and Anaissie E. *Clinical Infectious Diseases* 2009;49(8):1211–15.
32. Medical Scientific Advisory Group (MSAG) to the Myeloma Foundation of Australia (MFA). (2017). Clinical Practice Guideline Multiple Myeloma. Available at: <http://myeloma.org.au/wp-content/uploads/sites/2/2017/05/MSAG-Clinical-Practice-Guideline-Myeloma-V4-March-2017.pdf>.
33. Colson K, Doss DS, Swift R, et al. *Clinical Journal of Oncology Nursing* 2004;8(5):473–80.
34. Snowden JA, Greenfield DM, Bird JM, et al. *British Journal of Haematology* 2017;176(6):888–907.
35. Editor Preedy, V.R. Diet and Nutrition in Palliative Care. 2008. CRC Press.
36. Tariman J, Love G, McCullagh E, Sandifer S. *Clinical Journal of Oncology Nursing* 2008;12(30):29–36.
37. Cairo MS, Coiffier B, Reiter A, Younes A. *British Journal of Haematology* 2010;149:578–86.

APPENDIX

Appendix I: Tools and resources for nurses and patients

A. Neurotoxicity assessment tools

Examples of tools designed for nurses to assist in the evaluation of neurotoxicity and PN based on patient responses.

- Functional Assessment of Chronic Illness Therapy Neurotoxicity Questionnaire (FACT&GOG-Ntx)
Available at: <http://www.facit.org/FACITOrg/Questionnaires>
- EORTC Quality of Life Questionnaires Chemotherapy-Induced Peripheral Neuropathy (EORTC QLQ-CIPN20)
Available at: <http://groups.eortc.be/qol/chemotherapy-induced-peripheral-neuropathy-eortc-qlq-cipn20>
- Cancer Institute NSW EviQ (2017) Supporting Document – Peripheral Neuropathy
Available at: <https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/neurological-and-sensory/1743-peripheral-neuropathy#4589>
- National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) vs 4.
Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

B. Patient education and information

Links to online resources for MM patients.

- Myeloma: A Comprehensive Guide
Available at: <http://myeloma.org.au/information/>
- A guide to understanding myeloma tests and investigations
Available at: <https://www.hsanz.org.au/hsanz-nurses-group.asp>
- Managing Peripheral Neuropathy: A guide for People with Myeloma
Available at: <http://myeloma.org.au/information/>
- Information pathway for myeloma patients
Available at: <https://www.hsanz.org.au/hsanz-nurses-group.asp>
- Bortezomib treatment factsheets
Available at: <https://www.eviq.org.au/patients-and-carers/anticancer-drug-treatments/myeloma>
- Bortezomib treatment schedule
Available at: <https://www.hsanz.org.au/hsanz-nurses-group.asp>

