ABOUT THE AUTHORS

Jill Lacey, BSc, BSP, ACPR
Jill obtained a Bachelor in Pharmacy degree from the University of Saskatchewan in 2008 and then completed an accredited pharmacy residency program. She has been working in malignant hematology since 2010, with both inpatient and outpatient experience. Jill has been the Senior Hematology Pharmacist at the Saskatoon Cancer Centre since 2019.

Joanne Hewitt, PhD, NP
Dr. Joanne Hewitt is a doctoral prepared oncology nurse practitioner with a focus on multiple myeloma and plasma cell dyscrasias at the Cross Cancer Institute in Edmonton, Alberta. Her Interests include research activities, staff and patient education, and mentorship. She received the 2021 CANO Pfizer Award of Excellence in Nursing Leadership.

Jennifer L. Daley-Morris RPh, B.Pharm
Jennifer Daley-Morris is currently the Manager of the Oncology Pharmacy and Systemic Therapy Suite at the Stronach Regional Cancer Centre at Southlake in Newmarket, Ontario.

Judith James, RN, BSc
Judith James is currently a Research Nurse Coordinator at the QEII Health Sciences Center in Halifax, Nova Scotia. Judith has 27 years of nursing experience in the field of Hematology/Oncology, and for the last 10 years has focused her career on Hematology Research.

Jonathan Stevens, B.Pharm, ACPR
Jonathan Stevens is a graduate from the Memorial University School of Pharmacy and completed a hospital pharmacy residency at the Saint John Regional Hospital. He holds a clinical practice in outpatient hematology focusing on patient education, monitoring and toxicity management. He is working towards his PharmD at Memorial University.

Olivier Blaizel, B.Pharm
Olivier Blaizel graduated from Université de Montréal in 1996. After practicing for two years in community pharmacies, he turned to hospital pharmacy practice. He is now at Charles Lemoyne Hospital for nearly 20 years where he is coordinator of the oncology pharmacy since 2004. His practice focuses mainly on outpatients but he also works with patients on the hospital ward.

EXPERT CLINICAL FRAMEWORK REPORT: MANAGEMENT OF ADVERSE EVENTS RELATED TO NOVEL THERAPIES FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM)

Jill Lacey, BSc, BSP, ACPR[1], Joanne Hewitt, PhD, NP[2], Jennifer L. Daley-Morris[3] RPh, B.Pharm, Judith James, RN, BSc[4], Jonathan Stevens, B.Pharm, ACPR[5], Olivier Blaizel, B.Pharm[6]

1. *Senior hematology pharmacist, Saskatchewan Cancer Agency, Saskatoon, SK*
2. *Nurse practitioner, Cancer Care Alberta, Cross Cancer Institute, Edmonton, AB*
3. *Manager oncology pharmacy and systemic therapy suite, Southlake Regional Health Centre, Newmarket, ON*
4. *Research nurse coordinator, Capital District Health Authority, Halifax, NS*
5. *Clinical pharmacist in hematology, Saint John Regional Hospital, Saint John, NB*
6. *Pharmacist, Charles Lemoyne Hospital, Longueuil, QC*

Introduction

Multiple Myeloma (MM) is a malignancy of the plasma cells accumulating in the bone marrow. MM develops stepwise from the premalignant conditions, monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM).

The Canadian Cancer Society estimates that in 2022 4,000 Canadians will be diagnosed, and 1,650 will die from MM.[1] Survival rates have improved over the years with the development of novel treatment strategies, including proteasome inhibitors (PI), immunomodulatory drugs (IMiDs), targeted antibody and cellular therapies, and a selective inhibitor of nuclear export (SINE), as well as with the use of combinations of drugs. Although a number of patients will have a durable response following high-dose chemotherapy and autologous stem cell transplant (ASCT), MM remains an incurable malignancy with the majority of patients relapsing and eventually developing refractory disease (RRMM).

Collaborative environments, in which pharmacists work with hematologists/oncologists, nurse practitioners, and supportive care teams, have been shown to improve adherence to the treatment plan.[2] Prescription of appropriate prophylaxis in combination with various treatment strategies may reduce the number and duration of treatment delays.[2] Intensified clinical and pharmaceutical care, including medication management and structured patient counseling for patients on oral anticancer drugs, has been shown to reduce the number of medication errors and severe side effects while improving the patient's treatment experience.[3] Nurses play a vital role in the management of toxicities as they educate, support, and advocate for patients.[4] This report discusses the management of adverse events (AEs) related to both established agents and novel therapies for the optimal management of patients with RRMM (see **Table 1**). Established and novel therapies are often used in combination, which presents the potential for overlapping toxicities. The optimal combination therapies including the sequencing of various regimens are yet to be determined. Basic research and clinical trials with investigational agents are ongoing in an effort to improve both the depth and duration of response in newly diagnosed patients and those with RRMM with the aim of finding the best treatment options for every patient.

Proteasome Inhibitors (PI)

Bortezomib is a first-generation PI that can be used as a single agent, but is generally combined with dexamethasone, chemotherapy, IMiDs (lenalidomide and pomalidomide), or novel agents such as daratumumab and selinexor. The most common AEs associated with bortezomib are hematologic such as thrombocytopenia (43%), anemia (32%), as well as gastrointestinal, including nausea (64%), vomiting (36%), anorexia (43%), constipation (37%; often early in treatment), and diarrhea (51%; often later in treatment). Furthermore, patients may experience fatigue (65%), peripheral neuropathy (PN; 37%), pyrexia (36%), peripheral edema (25%), dyspnea (22%), and reactivation of Herpes zoster virus (13%) for which antiviral prophylaxis is necessary.[5]

Methods

- **Relevant literature for this framework was selected by the expert authors**
- **Included therapies were selected on basis of availability/approval in Canada**
- **Management strategies were based on relevant literature and clinical experience of expert authors**

Peripheral neuropathy is a toxicity that may be dose-limiting. PN has a negative impact on the quality of life (QoL) and daily activities of patients and can present itself as hyperesthesia, hypoesthesia, paresthesia, neuropathic pain, or neuropathic weakness.[5] The risk of PN has been decreased by administrating the drug subcutaneously (sc) instead of by intravenous (iv) administration, and by providing weekly dosing, instead of twice weekly dosing, as was originally described. This change in administration has been shown not to impact efficacy.[6] However, with this route of administration, up to 33% of patients still develop PN with bortezomib. This may limit future use of bortezomib in other treatment lines or use of other drugs also causing PN. It is essential that patients are aware so that they can notify their health care team if they develop neuropathic pain, as it can arise suddenly.

Therefore, for the best management of PN, patient education, neurological assessments, and patient-reported outcomes (PRO) before treatment and after each cycle of treatment allow for early detection and management when symptoms are more likely to be reversible.[5] Discontinuing or reducing the dose of bortezomib may reverse or lessen symptoms. Gabapentin or pregabalin is often useful in treating symptoms. Duloxetine may also improve pain and QoL in patients. Non-pharmacologic interventions such as acupuncture, trans-electrical nerve stimulation (TENS), exercise, and physiotherapy may be helpful in managing PN. It is important to rule out deficiencies in vitamin B12, magnesium, and potassium.[7]

Carfilzomib and ixazomib are second-generation PIs, which have less off-target activity than bortezomib.[8,9] However, carfilzomib is associated with cardiotoxicities, most of which are reversible, such as hypertension (in 67.4% of patients with 34.8% grade ≥2), congestive heart failure, and coronary artery disease, with 12% of patients presenting with a reduction of left ventricular ejection fraction (LVEF) by ≥20%.[8,10,11] Weekly dosing, instead of twice weekly dosing, decreases the risk of cardiovascular toxicities, and has the additional benefit that patients require fewer visits to the treatment centre. The risk of cardiovascular complications is higher in those with a history of cardiovascular disease, while no association has been found regarding dose, duration of infusion, or previous treatments.[8] Therefore, patients should be assessed for cardiovascular risk before treatment.[8] For hypertension, regular blood pressure and fluid overload monitoring before each infusion is required.[10]

When cardiovascular toxicities occur, patients should be appropriately assessed. Carfilzomib treatment and fluid administration should be temporarily paused for toxicities of grade ≥2, and supportive treatment, such as anti-hypertensives, should be provided, as well as serial electrocardiograms (ECGs) where required. Most patients can be retreated at lower doses (decreasing by one dose level) at an infusion time of at least 30 minutes. However, after dose reduction, cardiovascular toxicities may recur in some patients. In that situation, treatment with this PI should be discontinued permanently.[8,10,12]

Renal toxicity has been reported for carfilzomib in approximately 17% of patients. The toxicity can consist of thrombotic microangiopathy, albuminuria, and acute kidney injury. Dose discontinuation and dose reductions may be required to manage this toxicity.[8,13] A sodium chloride 250-500 mL bolus pre and post dosage should be given for cycle 1 to prevent renal toxicities and infusion reactions. If cardiovascular toxicities occur or if the patient has a higher risk of congestive heart failure, boluses should be stopped after cycle 1. Those with an estimated glomerular filtration rate (eGFR) <30 mL/min, attributed to the PI, should receive a dose reduction.[14] Bortezomib can be safely administered to patients on dialysis.[14]

Key Takeaways:

- ✓ **The first-generation PI bortezomib is associated with hematological and gastrointestinal AEs.**
- ✓ **Bortezomib may cause dose-limiting peripheral neuropathy.**
- ✓ **Second-generation PIs carfilzomib and ixazomib have less off-target effects than bortezomib.**
- ✓ **Carfilzomib is associated with reversible cardiotoxicities.**

Immunomodulatory drugs (IMiDs)

Lenalidomide and pomalidomide are IMiDs that are structural analogs of thalidomide, with an improved AE profile on dimensions such as constipation, anxiety and fatigue.[15,16] Common AEs include rash, diarrhea, constipation, neutropenia, anemia, thrombocytopenia, infection, and fatigue.[17] To prevent embryo-fetal exposure, IMiDs are only available in Canada through controlled distribution programs.

Neutropenia and thrombocytopenia are common AEs related to lenalidomide use, which can be managed with dose and schedule modifications. Those with severe neutropenia or who experience febrile neutropenia may be treated with granulocyte colony-stimulating factor (G-CSF, filgrastim).[4] Fatigue can be managed by education on sleep hygiene, sleep disturbance assessment, exercise programs, treatment of anemia, and the use of stimulants.[4]

Rash can be treated with topical steroid creams, oral antihistamines, or in severe cases, with dose modification, interruption, or desensitization protocols.[17]

Lenalidomide-induced diarrhea is related to bile salt malabsorption and, as such, responds well to bile acid sequestrants, such as cholestyramine or colesevelam.[17]

While uncommon, pulmonary toxicities have been reported in patients receiving IMiDs. These toxicities can develop abruptly at any time after treatment initiation. Patients with pulmonary toxicity can be managed by discontinuing the IMiD and/or treatment with corticosteroids. Empiric antibiotics should be started until infectious causes are excluded. Symptoms generally resolve upon IMiD discontinuation.[15] If the health care team determines it is safe to resume, treatment with IMiDs should be restarted at a lower dose.

Patients treated with thalidomide, lenalidomide, or pomalidomide combined with steroids and cytotoxic agents are at a higher risk of venous thromboembolic events (VTE). Concurrent use of EPO growth factors also increases VTE risk in patients treated with IMiDs. Patients should be assessed for risk, and thromboprophylaxis started before treatment. The specific pharmacological intervention [low dose ASA, low molecular weight heparin (LMWH), or warfarin] recommended will depend on an assessment of the individual patient's risk factors. Those who are already on anticoagulation should remain on the same medication dosage and regimen. Additional interventions such as sequential compression devices, anti-embolism stockings, and exercise may be recommended. Patients who develop VTE while on prophylaxis should receive therapeutic doses of LMWH, warfarin, or direct oral anticoagulants, and IMiD use should be paused. Once clinical stability is re-established, IMiD use can be continued at the original or lower dose, based on risk assessment, and therapeutic anticoagulation should be continued for as long as patients are on treatment for MM.[4,7,12] Furthermore, referral to a cancer-associated thrombosis program can be considered if available. The risk of second primary malignancies is increased in those treated with lenalidomide in specific settings, such as when lenalidomide is used post high- dose melphalan for ASCT and when melphalan is dosed in combination with lenalidomide. In other contexts, there is no elevation of secondary cancer risk with lenalidomide; however, the risk is multifactorial and not only attributable to therapy.[18]

Key Takeaways:

- ✓ **IMiDs lenalidomide and pomalidomide are associated with hematological and gastrointestinal AEs, neutropenia is common for patients on lenalidomide.**
- ✓ **Pulmonary toxicities may occur with IMiD use.**
- ✓ **IMiDs combined with steroids and cytotoxic agents increase the risk of venous thromboembolic events.**

Monoclonal antibodies

Anti-CD38 antibodies

Daratumumab is the first-in-class CD38-targeting monoclonal IgG1 antibody. Due to the expression of CD38 on various immune cells (e.g. plasma cells, natural killer (NK) cells), treatment with this antibody impairs and humoral immunity and increases the risk of infections, with 39% of patients developing infections after treatment, which can be viral, bacterial, or a combination of both.[19]

Therefore, the use of antimicrobial treatment as prophylaxis for infections should be considered for all patients on anti-CD38 antibodies, herpes zoster prophylaxis should be routinely used, and patients should be educated on infection prevention and actively monitored for infections.[19,20] Other management considerations are vaccines given before treatment initiation where possible, and monthly subcutaneous or intravenous prophylactic immunoglobulin (Ig) replacement is recommended for those with ≥ 2 infections per year.[4,7] Vaccines targeting seasonal influenza should be considered, even though patients undergoing treatment may have reduced responses to this vaccine. Additionally, patients should be vaccinated for *Streptococcus pneumonia, Haemophilus influenza* type b and during the current COVID-19 pandemic, SARS-CoV-2 vaccinations should also be considered, though limited information about efficacy is currently available. Even when patients receive the SHINGRIX vaccine, herpes zoster antiviral prophylaxis is advised as vaccination is less effective in immunocompromised patients.[7]

Daratumumab may be used in combination with a PI, IMiD, and dexamethasone. Isatuximab is another anti-CD38 monoclonal antibody that is used in combination with pomalidomide and dexamethasone. These isatuximab-containing combinations are generally well tolerated and have manageable toxicity profiles.[20,21] Respiratory infections [upper respiratory tract infection (55%), pneumonia (30%), and bronchitis (25%)] are also common for isatuximab and can occur with dyspnea.[20]

Infusion-related reactions (IRRs) are relatively common (45-50%) and almost always occur at the first daratumumab or isatuximab intravenous infusion. IRRs can be managed with pre- and post-infusion treatment with antihistamines, corticosteroids, montelukast, short-acting beta-2 agonists, and acetaminophen.[21] Slowing the rate or pausing the infusion during the initial infusion in the event of IRR in addition to repeating the above-mentioned medications can alleviate symptoms. Another option that is increasingly used is to give daratumumab subcutaneously, which is convenient as it only takes a few minutes to administer and has been shown to be non-inferior to intravenous administration, while significantly reducing grade 3 IRRs.[21]

For patients with chronic obstructive pulmonary disease (COPD) the use of post-injection short and long-acting bronchodilators and inhaled corticosteroids should be considered, as well as pre-treatment with montelukast.[22]

Other AEs associated with daratumumab are mostly hematological, including anemia, neutropenia, thrombocytopenia, fatigue, and pyrexia.[21] Given that daratumumab and isatuximab treatment interferes with blood compatibility testing due to CD38 expression on red blood cells, red blood cell phenotyping is recommended before the start of treatment to prevent delays when blood transfusions are required during treatment. Cardiovascular events include hypertension and cardiac failure.[12,22] The use of filgrastim may be considered to treat neutropenia.

The risk of secondary primary malignancies is increased in patients receiving isatuximab or daratumumab combination treatments, with a risk of skin cancer at 4% for those receiving this treatment, while this risk is compared with 1.5% for all patients regardless of treatment modality, and a risk of other solid tumors of 1.8% vs. 1.5% for all patients.[20,22] It is important for patients and clinicians to be aware of this risk, to encourage annual cancer screenings, and patients should receive appropriate treatment for any second primary malignancies.

Adverse event	Drug or drug class	Prevention	Management
Hematological AE			
-Thrombocytopenia -Neutropenia -Anemia	Bortezomib, Carfilzomib, Ixazomib, IMiDs, Daratumumab, Isatuximab, Belantamab mafodotin, Selinexor, Idecabtagene vicleucel		• Dose and schedule modifications • G-CSF (neutropenia) • Red blood cell transfusion (anemia) • Platelet transfusion (thrombocytopenia)
Cardiovascular AE			
-Hypertension -Hypotension -Congestive Heart Failure -Coronary artery disease	Carfilzomib Idecabtagene vicleucel	• Weekly dosing • Assess for cardiovascular risk • Blood pressure/fluid overload monitoring	• Discontinuation • Anti-hypertensives • Dose reduction
-Venous Thromboembolic Events	IMiD plus steroids and/or cytotoxic agents	• thromboprophylaxis	• LMWH, warfarin, or direct oral anticoagulants • Discontinuation
Peripheral neuropathy	Bortezomib Ixazomib	• sc drug administration • weekly dosing	• Discontinuation or dose reduction • Duloxetine, Gabapentin, Pregabalin • Exercise/acupuncture/ TENS/ physiotherapy
Neurological toxicities			
-Dizziness -Syncope -Depressed Level of Consciousness -Vertigo -Amnesia -Mental State Changes	lenalidomide pomalidomide bortezomib carfilzomib daratumumab isatuximab selinexor	• Advise to refrain from driving or engaging in hazardous occupations/ activities	• Optimize hydration status, hemoglobin levels, and concomitant medications • Institute fall precautions
Gastrointestinal AE			
-Diarrhea -Nausea/Vomiting -Decreased Appetite -Weight Loss	Selinexor Lenalidomide Bortezomib Carfilzomib Ixazomib Belantamab mafodotin Idecabtagene vicleucel	• Prophylactic use of steroids and 5-HT3 receptor antagonists and loperamide • Olanzapine and NK1 receptor antagonists • Daily weight checks and patient education • Monitor hydration status	• Bile acid sequestrants (lenalidomide-induced diarrhea) • Anti-emetic agents • Dose reduction
Hyponatremia	Selinexor		• Salt intake
Renal toxicity	Carfilzomib Ixazomib		• Dose reduction
Infections	Daratumumab Isatuximab Bortezomib Carfilzomib Ixazomib Belantamab Mafodotin Selinexor Idecabtagene vicleucel	• Infection prevention education • Vaccination • Herpes zoster prophylaxis • Prophylactic Ig replacement	• Empiric antibiotics • Antivirals
Ocular Toxicity			
-Corneal Disease -Visual Acuity Changes -Photophobia -Blurred Vision	Belantamab mafodotin	• Ophthalmic exam at baseline and before every cycle • Patient and health care team awareness • No contact lenses during treatment	• Ophthalmic exam • Dose interruption • Dose reduction • Lubricant drops/eye masks/ vasoconstrictors
Pulmonary Toxicity	IMiDs Carfilzomib		• Discontinuation • Corticosteroids • Dose reduction
-Patients with COPD	Daratumumab	• Montelukast	• Post-injection short and long-acting bronchodilators • Inhaled corticosteroids
Rash	IMiDs Bortezomib Ixazomib		• Topical steroid creams • Oral antihistamines • Dose modification /interruption • Desensitization protocols (IMiDs)
Fatigue	IMiDs Daratumumab Isatuximab Bortezomib Carfilzomib Belantamab mafodotin Selinexor Idecabtagene vicleucel	• Education on sleep hygiene • Exercise	• Stimulants • Treatment of anemia • Take IMiDs in evening/at bedtime
Infusion-Related Reactions	Daratumumab Isatuximab Belantamab mafodotin	• Pre-medicate with antihistamines, corticosteroids, montelukast, acetaminophen • Reduce infusion rate • sc administration	• Antihistamines, corticosteroids, acetaminophen • Reduce infusion rate • Short acting Beta-2 agonists (salbutamol)
CRS	Idecabtagene vicleucel		• Antipyretics and fluids • Vasopressors • Tociluzimab +/- corticosteroids • Dexamethasone • Maintain a high level of suspicion for underlying infection • Siltuximab or anakinra
CRS/MAS	Idecabtagene vicleucel		• Anakinra + corticosteroids
ICANS	Idecabtagene vicleucel		• Corticosteroids • Levetiracetam or benzodiazepines (seizure treatment) • Siltuximab and anakinra

Table 1. Common adverse events and management strategies for relapsed/refractory multiple myeloma.

AE: adverse event; COPD: chronic obstructive pulmonary disease; CRS: cytokine release syndrome; G-CSF: granulocyte colony-stimulating factor; ICANS: immune effector cell-associated neurotoxicity syndrome; IMiD: immunomodulatory drug; LMWH: low molecular weight heparin; mAb: monoclonal antibody; MAS: macrophage activation syndrome; PI: proteasome inhibitor; sc: subcutaneous.

Belantamab Mafodotin

Belantamab mafodotin is a first-in-class antibody-drug conjugate targeting B cell maturation antigen (BCMA) with a high specificity for MM cells. Belantamab mafadotin is not approved by Health Canada, but it is currently available through Health Canada's Special Access Program for patients who have previously been treated with at least four prior lines of therapy. The antibody delivers the cytotoxic payload monomethyl auristatin-F (MMAF) directly to MM cells, which induces apoptosis of the tumor cells.[23]

Adverse events associated with this drug include ocular toxicity, thrombocytopenia, anemia, IRRs, pyrexia, and fetal risk.[23] Ocular toxicity includes corneal disease (e.g. keratopathy, microcysts), changes in visual acuity, photophobia, and blurred vision. There is a high risk (≥20%) of keratopathy, and therefore patients must undergo an ophthalmic exam by an ophthalmologist or optometrist prior to (baseline exam) and during therapy (before each cycle where required) to determine baseline vision and monitor possible ocular adverse eye effects.[23,24] It is essential that hematologists, oncologists, and the entire care team are aware of this ocular risk, that patients are educated about the risk, and that symptoms are accurately monitored and assessed. Contact lenses should not be worn during treatment. When toxicity occurs, including blurry vision, dry eyes, or corneal ulcers, an ophthalmic exam should be performed, and dosing should be reduced or interrupted based on the most severe finding. In our clinical experience, interruption of treatment may be long (4-5 months) before ophthalmology exam findings return to baseline. Dose interruptions will allow for the regeneration of corneal epithelial cells. Dose modifications can be made based on the Keratopathy and Visual Acuity (KVA) scale, which is available in the prescribing information of belantamab mafodotin. Furthermore, preservative-free lubricant drops can be used; however, these drops are expensive and our clinical experience is that patients tend to reduce dosing to reduce cost. Other treatment options include cooling eye masks or vasoconstrictor drugs that can be administered at the start of the infusion, though benefits have not been confirmed yet. Long-term use of topical steroids may cause AEs and is not advised. Most patients are expected to recover from corneal AEs, with 50% of corneal events resolving within approximately 35 days.[7,23-25] Trials are ongoing to evaluate various dosing and treatment schedules with the aim of reducing ocular toxicities while maintaining efficacy.

Key Takeaways:

- ✓ **Anti-CD38 monoclonal antibodies daratumumab and isatuximab are associated with reduced immune function and increased risk of infections.**
- ✓ **Infusion-related reactions are common with daratumumab and isatuximab, and occurs mostly at first infusion.**
- ✓ **Belantamab mafodotin is associated with a high risk of ocular toxicity.**

Selinexor

Selinexor is a first-in-class oral selective inhibitor of nuclear export (SINE) and works by binding to exportin-1 (XPO1). XPO1 is involved in cellular transport of tumor suppressor proteins (TSPs), such as p53, and mRNA encoding for oncogenic proteins. This leads to nuclear accumulation of TSPs, cell cycle arrest, and apoptotic cell death. Selinexor is indicated in combination with bortezomib and dexamethasone (SVd) for adult patients who have received at least one prior line of therapy. At the time of publication of this expert clinical framework, selinexor has been recommended for reimbursement by CADTH and is available via a market access program for the approved indication and is reimbursed by some private insurance carriers. The approval was based on data from the BOSTON study a Phase 3, randomized, open-label study of patients with multiple myeloma who had received 1-3 prior therapies that compared patients receiving selinexor + dexamethasone with patients receiving bortezomib and dexamethasone. Treatment with selinexor (100 mg/week), bortezomib (1.3 mg/m^2/week), and dexamethasone (20 mg twice/week) was shown to result in an overall response rate (ORR) of 76.4% with a median progression-free survival (PFS) of 13.93 months compared to 9.46 months for bortezomib and dexamethasone.[27] In an exploratory subgroup analysis of BOSTON, efficacy was observed in multiple subgroups, including patients with renal impairment, elderly, and frail patients, as well as those who had previously received lenalidomide, bortezomib, carfilzomib. ixazomib and daratumumab.[28] Furthermore, a sub-analysis comparing the patient population with high-risk cytogenetics (presence of del[17p], t[4;14], t[14;16], and ≥ 4 copies of amp1q21; N=70) to those with standard risk (N=261) revealed a similar AE profile, while showing efficacy. In the high-risk population, the median PFS was 12.91 months (vs. 8.61 months for Vd) and the ORR was 78.6% (vs. 57.7% for Vd). PFS and ORR were similar to those in the standard risk population (PFS 16.62 months, ORR 75.2%). These data suggest this regimen including selinexor may be able to be effectively used in difficult-to-treat MM populations.[29]

Treatment with selinexor requires supportive care, with AEs including fatigue, nausea, and decreased appetite, as well as hyponatremia which requires electrolyte monitoring.[30] However, with appropriate supportive care and dose modification, or adverse reactions selinexor-containing regimens are tolerated and effective.

A proactive approach is required to manage the GI tract toxicities, as symptoms can intensify quickly. Prophylactic prevention of nausea is more effective than starting anti-emetics after symptoms arise. Prophylactic use of 5-HT3 receptor antagonists should be used, along with olanzapine and/or an NK1 receptor antagonists, or Akynzeo® (combination of 5-HT3 antagonist (palonosetron) and NK1 receptor antagonist (netupitant); anti-emetics can be tapered off or discontinued over time but are particularly helpful in the first two cycles.[30]

Weight loss can occur in a small subset of patients; patients should be instructed to weigh themselves daily and notify their HCP if they experience weight loss. Interventions include patient education on nutrition and patients should be encouraged to eat high-calorie food and snacks to maintain their weight. Supplements like nutritional

drinks can be added if appetite and weight cannot be maintained. Appetite stimulants are not recommended but can be considered. Consultation by a registered dietician for patient education and follow-up can be helpful to prevent and treat weight loss.

In the Phase III study assessing selinexor, bortezomib, and dexamethasone, dose reductions were common, with 126/195 subjects having dose reductions from the original protocol of 100 mg/week of selinexor. The mean dose received by patients in BOSTON accounting for dose reductions was 80 mg /week. The efficacy in this subgroup was observed in patients on XVd who underwent dose reduction. The median duration of treatment (34.5 weeks vs. 20.0 weeks), median PFS (16.6 months vs. 9.2 months), and ORR (81.7% vs. 66.7%) were higher in the group that received dose reductions. GI tract AEs reduced after dose reduction, including nausea (31.6% vs. 7.3%), decreased appetite (21.5% vs. 6.4%), diarrhea (12.9% vs. 5.2%), and weight loss (9.0% vs. 5.9%).[32] Therefore, dose reductions can be used to manage toxicities while maintaining efficacy in response to adverse reactions **(Figure 1)**. Both the dosage and the schedule can be modified. Hyponatremia may occur and can be prevented by adequate fluid intake. To manage hyponatremia, sodium tablets, salt-containing drinks or food, or intravenous saline can be used in severe cases. Selinexor should be stopped when sodium drops below 130 mmol/L and resumed at one dose level lower when that level is corrected.[30]

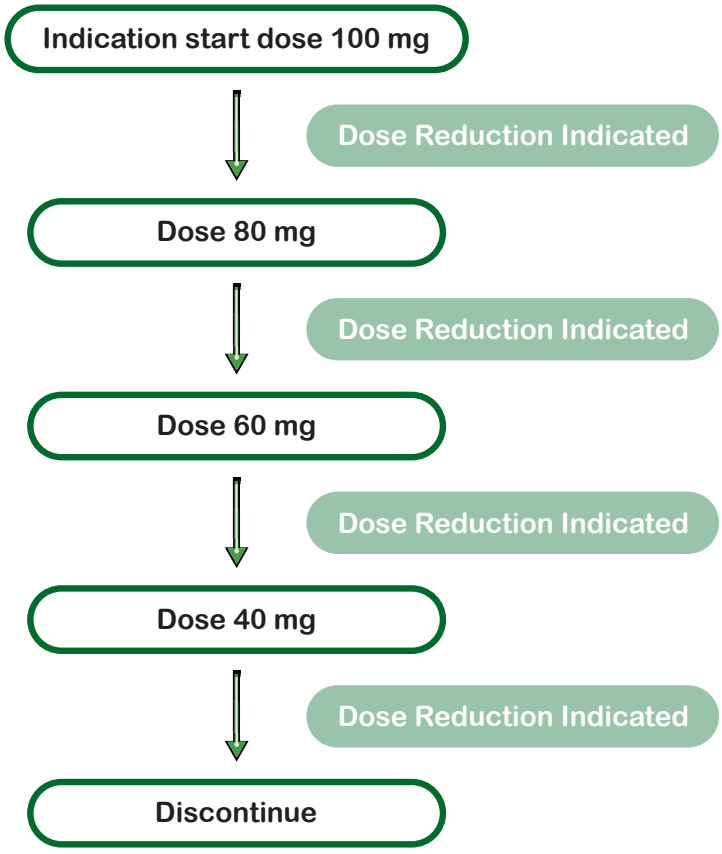

Figure 1: *Flow chart for selinexor dose adjustments for adverse reactions when combined with bortezomib and dexamethasone.*[31]

The most common hematological toxicity is thrombocytopenia, which should be monitored with regular lab work. Patients should be educated to watch for bleeding and to notify their HCP with any concerns. If required, platelet transfusions can be administered. Thrombocytopenia occurs in a dose-dependent fashion; therefore, interruption and/or dose reduction can reduce the severity of this toxicity. If required, red blood cell transfusions may be given for symptomatic anemia. Interventions for neutropenia include the use of filgrastim and/or selinexor dose reductions in the case of grade 3-4 toxicity.[24,30] Education on exercise and sleep hygiene is essential to address fatigue and asthenia. Stimulants such as methylphenidate may be considered.[30] The combination of selinexor with other drugs including bortezomib show similar safety profiles as the single agents, and the same strategies for each of the individual drugs should be used to manage toxicities in the combination regimens.[33,34]

Key Takeaways:

- ✓ **Selinexor is a novel oral exportin-1 inhibitor**
- ✓ **Gastrointestinal tract toxicities are common and require a proactive approach.**
- ✓ **Weekly dosing of selinexor and bortezomib in the SVd regimen instead of twice weekly dosing has improved tolerability.**
- ✓ **Dose modifications, including dose reductions, can be utilized to manage toxicities without compromising efficacy**
- ✓ **In exploratory sub-group analyses, efficacy in high-risk (including del17p) and difficult-to-treat populations, such as elderly and/or frail patients, as well as those with renal impairment and lenalidomide-refractory disease was observed.**

Chimeric antigen receptor (CAR) T cell therapy

The anti-BCMA CAR-T cell therapy idecabtagene vicleucel has been approved for RRMM and other anti-BCMA-CAR-T cell therapies are in clinical development. CAR-T cell treatment is generally provided in specialized centers but may expand to more centers in the future. As this therapy can come with significant AEs, assessing patient eligibility should include medical history, performance status, age, life expectancy, infections, prior treatments, and history of central nervous system involvement to ensure patient fitness.

This treatment requires lymphodepleting conditioning with fludarabine and cyclophosphamide before CAR-T cell infusion, which has several potential complications: pancytopenia, immunosuppression, infection, neurotoxicity, hemorrhagic cystitis, pericarditis, and secondary malignancies. Renal and hepatic impairments should be managed by dose modifications, and active infections should be controlled before lymphodepletion.[35]

Bridging therapy can be administered in the period between leukapheresis and CAR-T cell administration (manufacturing time), to reduce disease burden and improve CAR-T efficacy as well as reduce potential toxicities associated with CAR-T. Bridging therapies may consist of high or low-dose

chemotherapy, radiotherapy, or novel agents. Management of specific therapies should be considered during this time. Premedication before CAR-T infusion with acetaminophen and antihistamines is recommended, but no concurrent medication should be administered with the CAR-T cells.[35] Outpatient CAR-T cell infusion can be performed safely with clear policies, appropriate infrastructure, well-trained staff, and capacity for hospitalization at any time. If this is not available, a 14-day hospitalization after infusion is recommended.

Infusion reactions are rare but should be treated symptomatically, though corticosteroids should be avoided unless critical.[35] Active infections should be controlled before lymphodepletion. After lymphodepletion, patients are neutropenic. Therefore, when a fever arises, it should be assessed and immediately treated with empiric antimicrobial therapy.

Tumor lysis syndrome may occur and should be prevented and managed with standard local protocols.[35]

Cytokine release syndrome (CRS) is common (30-100%), with 10-30% of patients experiencing grade ≥ 3 CRS. Risk factors for high-grade CRS include tumor burden, infections, CAR-T cell dosing, and the intensity of the lymphodepleting regimen. CRS can occur within the first 14 days after infusion and may last 1-10 days. Empiric broad-spectrum intravenous antibiotics should be started until an infection is ruled out. CRS should be managed by antipyretics and fluids to treat symptoms, and tocilizumab with or without corticosteroids is the standard treatment. When two doses of tocilizumab fail, dexamethasone should be initiated. Corticosteroids should be tapered off rapidly once CRS is under control.[35] Tocilizumab increases the risk of occult sepsis and gastrointestinal perforation, which should be monitored. If CRS does not respond to treatment, alternative options include siltuximab and anakinra.

When fever persists despite tocilizumab use, and the patient experiences organomegaly cytopenia, hyperferrritenia, liver dysfunction, coagulopathy, and hypertriglyceridemia, there may be CRS/macrophage activation syndrome (MAS) overlap syndrome, for which anakinra can be used in combination with corticosteroids.[35]

Immune effector cell-associated neurotoxicity syndrome (ICANS) is less likely to occur with anti-BCMA CAR-T than with other CAR-T therapies; symptoms include tremors, confusion, agitation, seizures, dysphasia, and deterioration in handwriting. Onset is typically between day 3 and 5 after infusion and can occur concurrently with CRS, but delayed ICANS (> 3 weeks after infusion) has also been reported. Risk of high grade ICANS is higher in those receiving CAR-T products with CD28 co-stimulation domains or higher doses, and those having a higher tumor burden, pre-existing neurological conditions, thrombocytopenia, or severe CRS. Management includes corticosteroids with rapid taper, and seizures can be treated with levetiracetam and benzodiazepines. ICU transfer may be required.[35]

Cardiovascular toxicity occurs in 10-20% of patients, risk factors include grade > 2 CRS, high tumor burden, and pre-existing cardiac dysfunction. Cardiovascular assessment should be conducted before infusion, and risk-reducing strategies should be undertaken. Cardiovascular toxicities respond well to tocilizumab.[35]

Infections should be rapidly treated, and prophylaxis is warranted. Prolonged neutropenia can be treated with filgrastim.[35]

Key Takeaways:

- ✓ **CAR-T cell therapy is a novel therapy class associated with specific toxicities.**
- ✓ **Cytokine release syndrome is common and should be monitored and managed accurately.**
- ✓ **Immune effector cell-associated neurotoxicity syndrome is less likely to occur with current approved anti-BCMA CAR-T therapy.**

Conclusion

Novel therapeutics for RRMM come with new challenges for patient management. The management of toxicities associated with these therapies requires a multidisciplinary approach to address the many challenges **(Table 1)**. Effective education on potential toxicities and appropriate management ensures the best patient care and limits dose reductions and discontinuations. Pharmacists and nurses can play a crucial role in counseling and providing supportive care. Virtual clinics may provide personalized efficacy monitoring and patient counseling.[2,17] Clinical trials are continuously ongoing and will provide novel therapies, new combinations, and new treatment sequences to be considered for RRMM.

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