Clinical Guidance: Use of Belantamab Mafodotin in the Management of Relapsed/Refractory Multiple Myeloma

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Do	• **Extensions of dosing intervals are common:** For patients experiencing treatment response (partial response or better) after 3 cycles, consider increasing dose intervals to 8-12 weeks. If patients experience eye-related side effects, hold BELA dose until recovered to baseline, then increase dose interval to 8-12 weeks.[1] • **Cross-disciplinary collaboration with eye care professionals** is needed for effective management of BELA. • **Patient education** about potential side effects and the importance of adherence to monitoring schedules is essential. Patients will often require dose extensions or pauses without impact on efficacy.[1–3] • **Ophthalmologic monitoring should be performed before each planned dose of BELA** to detect and manage keratopathy.[2] Use the Vision-Related Anamnestic (VRA) tool at every dosing visit to monitor potential ocular symptoms.[1]
Stop	• **Delay BELA dose and eye exam** if a patient is experiencing ocular symptoms as assessed by the VRA tool. If symptoms are not improving after 8-12 weeks, request an eye exam.[1]
Consider	• **In patients with no risk factors**, eye exams can occur within two weeks following treatment initiation. • Ocular adverse events were **manageable and reversible** in most patients, with few patients discontinuing treatment as a result. Dose delays, reductions, and extensions between BELA doses led to recovery without affecting treatment efficacy. Seek an eye care consult if needed.[1–6]

Use of Antibody-Drug Conjugates and BCMA-Targeted Therapies in Relapsed/Refractory Multiple Myeloma

Relapsed/refractory multiple myeloma treatment is complex and rapidly evolving, aiming to prolong survival, improve quality of life, and control symptoms.[7] Increasing incidences of refractory disease at first relapse following frontline use of lenalidomide and anti-CD38 antibodies require new agents, such as those targeting B-cell maturation antigen (BCMA).[8–10] BCMA promotes survival and proliferation of long-lived plasma B cells, is nearly absent on naïve and memory B cells, and is commonly expressed at high levels in malignant plasma cells among multiple myeloma patients.[11–13]

Antibody-drug conjugates are a class of targeted therapies that combine a tumour-specific antigen antibody with a cytotoxic drug, in this case BCMA, thereby minimizing systemic toxicity and enhancing therapeutic efficacy.[10] Belantamab mafodotin (BELA) is the only drug in this class currently available in Canada, with others in early stage clinical trials.[14,15]

Belantamab Mafodotin Overview

BELA has a novel, multimodal mechanism of action that differs from other BCMA-targeted therapies by eliminating myeloma cells through direct cell kill and anti-multiple myeloma immune response.[5] It combines a monoclonal antibody that binds to BCMA, coupled with monomethyl auristatin F. The free cytotoxic agent is released inside the tumour cell, disrupting the microtubule network, leading to cell cycle arrest and apoptosis. BELA is used in adults following ⩾1 line of therapy in combination with dexamethasone and either bortezomib (BVd) or pomalidomide (BPd), due to their complementary anti-proliferative, pro-apoptotic mechanisms of action.[15–17]

Dosing, Monitoring, Prophylaxis, and Management of Adverse Events

Adverse events associated with BELA include ocular side effects (see next section), thrombocytopenia, neutropenia, infections, and infusion-related reactions.[15]

Dose modifications and extended administration schedules, especially in patients with a response to treatment, enable management of adverse events without negatively affecting treatment efficacy (see algorithm, next).[1–5]

Incidence of grade 3-4 adverse events[3,15]	BVd	BPd
Reduced visual acuity	59%	61%
Corneal examination findings (including keratopathy)	78%	66%
Fatigue	6%	8%
Infection (i.e. pneumonia)	12%	28%
Neutropenia	14%	58%
Thrombocytopenia	73%	38%
Infusion-related reactions	0%	1%

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Recommendations for Dosing of BELA

BELA Approved Dosing Schedule

BVd

Baseline: 2.5 mg/kg
Q3W: 2.5 mg/kg
Q3W: 2.5 mg/kg
Q3W: 2.5 mg/kg
Q3W: 2.5 mg/kg
Q3W: 2.5 mg/kg
*Q3W: 2.5 mg/kg
*Q3W: 2.5 mg/kg

Continue combination therapy for 8 cycles, then continue as single agent until disease progression or unacceptable toxicity

BPd

Baseline: 2.5 mg/kg
Q4W: 1.9 mg/kg
Q4W: 1.9 mg/kg
Q4W: 1.9 mg/kg
Q4W: 1.9 mg/kg
Q4W: 1.9 mg/kg
*Q4W: 1.9 mg/kg

Continue until disease progression or unacceptable toxicity

Ocular Monitoring

Eye Exam
Baseline: Within 3 weeks
Cycle: Within 2 weeks

Vision-Related Anamnestic tool
Use at every visit

Eye exam required prior to each dose, more frequently as clinically indicated, and promptly for new or worsening ocular symptoms. *If changes in vision or corneal signs are not observed at or before the sixth dose, eye exam frequency may be reduced to approximately every 3 months. Patients should report ocular symptoms promptly.

Eye-Related Side Effects

If adverse events occur, continue standard of care dosing for dexamethasone and bortezomib/pomalidomide and change BELA dosing:

HOLD dose until symptoms improve to ⩽Grade 1 → Q4W → Resume treatment at reduced dose:

- Grade 1:** Continue at current dose with close direct monitoring of clinical status
- Grade 2-3: BVd: 1.9 mg/kg Q3W; BPd: 1.9 mg/kg Q8W
- Grade 4:**:*** BVd: 1.9 mg/kg Q3W; BPd: 1.4 mg/kg Q8W

*** At the discretion of the prescriber*

****If symptoms are unresponsive, consider permanent discontinuation*

Practical Consideration: After 3 cycles with treatment response (partial response or better), consider dose extension

BVd/BPd

Baseline: 2.5 mg/kg
Q4W: 1.9 mg/kg
Q4W: 1.9 mg/kg
Q8-12W: 1.9 mg/kg
Q8-12W: 1.9 mg/kg

Continue until disease progression or unacceptable toxicity

If grade ⩾2 ocular adverse events occur, continue regular dosing of dexamethasone and bortezomib/pomalidomide and change BELA dosing:

BVd/BPd

HOLD dose until symptoms improve to ⩽G1 → Monitor Q4W with VRA. If symptoms are not improving by 8W / resolved by 12W, seek eye exam and continue to hold dose → Once symptoms improve to baseline, resume at extended dosing interval: G2=Q8W, G3= Q12W, G4 = Q⩾22W → If extensions do not resolve symptoms, consider dose reduction: G2/3=1.9 mg/kg; G4 = Discontinue or 1.4 mg/kg

Treatment response is not reduced if dosing interval is extended, and those who move to extended dosing regimens are unlikely to go to a more frequent dosing schedule. Do not reescalate dose after a reduction is made due to eye-related side effects. If symptoms don't improve after dose modification, additional eye exams are needed.

Eye-Related Side Effects[18]

BELA is associated with eye-related side effects due to its cytotoxic component, MMAF, which can accumulate in corneal epithelial cells through nonspecific uptake or diffusion, even though these cells do not express BCMA.

The most common reactions are dry eye, blurred vision, or a decline in visual acuity.[19] Keratopathies (a finding on slit lamp exam), such as superficial punctate keratopathy and microcyst-like deposits, may occur as a result of corneal epithelial cell apoptosis following internalization of BELA.[18]

Changes to vision were generally mild-to-moderate and transient, generally resolving with dose holds.[18]

Consult your eye care specialist for additional information or location-specific guidance.

Vision-Related Anamnestic (VRA) tool[1,5]

- Use at every appointment to assess eye symptoms to assess timing of the next BELA dose administration based on the vision-related anamnestic tool.
- Ask patients "During the last 24 hours, did you…":

"…feel sensitive to light?
"feel like your eyes were gritty, painful, or sore?"
"have blurred vision?"
"have problems in reading or driving due to eye problems?"
"have difficulty watching TV or working with a computer or smartphone due to eye problems?"

- If a patient answers "no" to all the questions, treatment is continued.
- If "yes", clarify duration of symptoms:
  4-<8 hours (minimal) *8-<12 hours (moderate)*
  12-<16 hours (substantial) *⩾16 hours (severe)*
- If symptoms impact activities of daily life or have lasted ⩾8 hours (moderate-severe), treatment should be delayed until symptom resolution. Monitor using VRA tool Q4W.
- If symptoms do not begin to improve within 8 weeks or not resolved by 12 weeks, seek an eye exam.

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Best Practices for Supportive Ocular Care

- Close collaboration with an eye specialist is essential.
- Eye exams (including visual acuity, slit lamp examination, and fundoscopy) are required initially to assess cataracts and monitor for keratopathies.
- Schedule eye exams in advance based on BELA dosing schedules.
- Patients should wear corrective vision during examinations.
- The severity of findings and change in Best Corrected Visual Acuity should be determined for each eye as compared to baseline.
- The worst severity for the most severely affected eye should be reported to the prescriber.
- Based on these findings, the prescriber may modify the BELA schedule and/or dose.

Advise Patients:

- You will receive eye exams, as side effects may occur.
- Do not use regular contact lenses until end of treatment.
- If undergoing cataract surgery, wait at least 1 cycle before resuming BELA treatment.
- Use caution when driving or operating machinery due to potential vision changes.
- Use preservative-free artificial tears at least 4 times a day during treatment.
- Eye-related side effects are transient, and vision usually recovers.
- Holding BELA doses for short durations to give eyes time to recover does not affect treatment efficacy.

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