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Unique Toxicities of Novel Myeloma Therapies: Focus on Belantamab Mafodotin, Talquetamab, and Selinexor

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Introduction

Recent survival improvements in patients with multiple myeloma are attributable largely to the introduction of three main drug classes, immunomodulatory drugs (IMIDs), proteasome inhibitors, and anti-CD38 monoclonal antibodies.[1] However, the majority of patients will inevitably develop resistance to all three drug classes, and survival in this setting has been historically poor.[2-3]

Several novel therapeutic classes exploiting new mechanisms of action (e.g., chimeric antigen receptor (CAR)-T cell therapy, bispecific antibodies, antibody-drug conjugates (ADC), and selective inhibitors of nuclear export) have shown high levels of activity in relapsed myeloma and promise to transform the treatment landscape.[4-5] However, these therapies have been associated with distinct toxicity profiles, with adverse effects that are uncommonly observed with conventional antimyeloma therapies. Given improvements in long-term disease control and survival with current therapies, treatment-related toxicity represents an increasingly important health burden in patients with myeloma, and the development of effective toxicity management strategies is required to minimize complications and ensure preserved quality of life.

The current article focuses on unique toxicities associated with three agents that have obtained recent approval for use in relapsed myeloma: belantamab mafodotin, an anti-B cell maturation antigen (BCMA) antibody-drug conjugate (ocular toxicity); talquetamab, an anti- G protein–coupled receptor class C group 5 member D (GPRC5D) bispecific antibody (oral and cutaneous toxicity); and selinexor, a selective inhibitor of nuclear export (hematological, gastrointestinal, and constitutional toxicity). Key trials for these agents are summarized in **Table 1**.

Belantamab mafodotin

Belantamab mafodotin (belamaf) is a first-in-class, humanized ADC targeting B-cell maturation antigen, a cell surface receptor ubiquitously expressed on myeloma plasma cells.[5] Phase 1/2 studies of single-agent

belamaf demonstrated significant activity in relapsed/refractory myeloma, though with adoption complicated by frequent ocular toxicity and lack of benefit over standard of care in a randomized trial.[6-7] The pivotal DREAMM-7/DREAMM-8 phase 3 trials demonstrated the benefit of belamaf-containing combination regimens in patients with relapsed myeloma after 1 or more prior lines of therapy, in comparison with standard-of-care regimens.[8-9] In the DREAMM-7 study, BVd (belamaf, bortezomib, dexamethasone) was associated with significant prolongation of progression-free survival (PFS) in comparison with DVd (daratumumab, bortezomib, dexamethasone) (median PFS 36.6 vs 13.4 months; hazard ratio [HR]: 0.41), with evidence of overall survival benefit on updated follow-up.[8,10] In the DREAMM-8 study, BPd (belamaf, pomalidomide, dexamethasone) demonstrated significant improvement in PFS in comparison with the standard-of-care PVd regimen (pomalidomide, bortezomib, dexamethasone) (12-month estimated PFS, 71% vs. 51%; HR: 0.52).[9] The BVd/BPd regimens are approved by Health Canada for use in relapsed multiple myeloma, with specific indications following the eligibility criteria of the DREAMM-7/8 studies.

Corneal epithelial toxicity is a known effect of ADC therapy and occurs frequently in patients receiving belamaf. Common ocular symptoms include dry eye, photophobia, and reduction in visual acuity, and are associated with microcystic changes in the corneal epithelium on ocular slit lamp examination.[11] The exact mechanisms of ocular toxicity remain uncertain, but have been hypothesized to relate to off-target uptake of the ADC in corneal epithelial cells and resultant apoptosis due to intracellular release of the monomethyl auristatin F (MMAF) payload. The incidence of all-grade and grade 3-4 ocular toxicity has ranged from 70–90% and 30–55% of patients, respectively, in prospective belamaf single-agent and combination trials.[6,8-9,12] Of note, pre-existing ocular conditions (e.g., cataracts, glaucoma, baseline visual acuity >20/50) have not been exclusion criteria from belamaf trials, and an association between baseline ocular conditions and an increased risk of ocular adverse events has not been consistently observed.[8-9,13]

Serial ophthalmological examinations were mandatory for patients receiving belamaf-containing regimens on the DREAMM-7/8 studies, and ophthalmic findings were graded based on a Keratopathy and Visual Acuity (KVA) scale incorporating corneal findings on ocular slit lamp exam and measured changes in best corrected visual acuity (BCVA) (**Tables 2 and 3**).[8-9,14] Protocol-based dose modifications in both trials were primarily based on ophthalmic exam findings, with dose delays until resolution and/or dose reduction required for patients with grade ≥2 findings. Overall, dose delays due to ocular toxicity occurred in 78/75% and dose reductions in 44/57% of patients on BVd/BPd, respectively, with the majority of patients experiencing a first event after the first 2 cycles of therapy. Patients commonly experienced multiple episodes of ophthalmic toxicity, with approximately 55% of patients with a grade ≥2 ophthalmic event in both studies experiencing three or more occurrences. However, ocular toxicity was reversible with treatment interruption in the majority of patients. In a pooled analysis of both studies, documented resolution had occurred in 83% of grade ≥2 ophthalmic events at the time of data cut-off with a median time to resolution of 12 weeks.[14] In patients with reduction of visual acuity to 20/50 in the DREAMM-7/8 studies, 85–95% had improvement of vision to baseline acuity, with a median time to resolution of 8–9 weeks; improvement occurred in all patients with reduction of visual acuity to 20/200 (1-2% of belamaf-treated patients in both studies).[8-9,14] Discontinuation of therapy due to ocular toxicity occurred in 9% of patients in both trials.

Belamaf dose delays and modifications led to a progressive lengthening of treatment interval in the DREAMM-7/8 studies, though without appearing to compromise efficacy. In both studies, the median interval between doses increased over time, from the initial protocol-specified intervals of 3–4 weeks to 8–12 weeks after the first 9 months.[14] However, among patients treated with BVd experiencing at least one extended dose delay (>2 cycles), median PFS was 36.6 months, similar to the overall BVd arm in DREAMM-7, and in the DREAMM-8 study, the estimated 12-month PFS was 90% in BPd-treated patients requiring at least one extended dose delay. Among patients requiring extended belamaf dose delays, 85–90% had already achieved at least a partial response prior to the first extended dose delay, with up to 90% subsequently achieving at least very good partial response (VGPR) following the delay.

Practical guidelines have been created for the management of belamaf-associated ocular

Study	Study Type	Population	Treatment	Response rate	PFS	OS	Toxicity
DREAMM-7[8]	Phase 3, randomized, open-label	Relapsed MM, at least 1 prior line of therapy (n=494)	**Standard arm (DVd)** Bortezomib 1.3 mg/m^2 SC, d. 1,4,8,11/21-day cycle), 8 cycles Dexamethasone 20 mg PO, day of/day after each bortezomib dose, 8 cycles Daratumumab 16 mg/kg IV, qweek cycles 1–3, q3 weeks cycles 4-8, q4 weeks cycle 9+, until progression **Experimental arm (BVd)** Bortezomib, per standard arm (above) Dexamethasone, per standard arm (above) Belantamab mafodotin 2.5 mg/kg IV, d.1 of 21-day cycle, until progression	***BVd vs. DVd*** **ORR:** 83 vs. 71% **VGPR:** 66 vs 46% **CR:** 35 vs.17% **MRD-negative rate:** 39 vs. 17%	***Median PFS:*** **BVd:** 36.6 months **DVd:** 13.4 months (HR: 0.41, p<0.001)	***18-month OS:*** **BVd:** 84% **DVd:** 73% (HR: 0.57, p=NS)	***Thrombocytopenia, grade 3–4*** **BVd:** 55% **DVd:** 35% ***Infection, grade 3–4*** **BVd:** 31% **DVd:** 20% ***Ocular adverse events, any-grade*** **BVd:** 79% **DVd:** 29% ***Ocular adverse events, grade 3–4*** **BVd:** 34% **DVd:** 3%
DREAMM-8[9]	Phase 3, randomized, open-label	Relapsed MM, at least 1 prior line of therapy, with previous lenalidomide exposure (n=302)	**Standard arm (PVd)** Bortezomib 1.3 mg/m^2 SC, d. 1,4,8,11/21-day cycle, cycles 1-8, then d. 1,8/21-day cycle, cycle 9 onwards, until progression Pomalidomide 4 mg PO, d. 1–14/21-day cycles, until progression Dexamethasone, 20 mg PO, day of/day after each bortezomib dose, until progression **Experimental arm (BPd)** Belantamab mafodotin 2.5 mg IV cycle 1, then 1.9 mg/kg IV q 4 weeks, cycle 2 onwards, until progression Pomalidomide 4mg PO, d 1–21/28-day cycle, until progression Dexamethasone 40 mg PO weekly, until progression	***BPd vs. PVd*** **ORR:** 77 vs. 72% **VGPR:** 64 vs.38% **CR:** 40 vs.16% **MRD-negative rate:** 32 vs. 5%	***12-mo. PFS*** **BPd:** 71% **PVd:** 51% (HR: 0.52, p<0.001)	***12-mo. OS*** **BPd:** 83% **PVd:** 76% (HR 0.77, p=NS)	***Thrombocytopenia, grade 3-4*** **BPd:** 24% **PVd:** 20% ***Infection, grade 3–4*** **BPd:** 49% **PVd:** 26% ***Ocular, all-grade*** **BPd:** 89% **PVd:** 30% ***Ocular, grade 3–4*** **BPd:** 43% **PVd:** 2%

Study	Study Type	Population	Treatment	Response rate	PFS	OS	Toxicity
MonumenTAL-1[20]	Phase 1–2	Relapsed MM, at least 3 prior lines of therapy, including IMID, proteasome inhibitor, and anti-CD38 monoclonal antibody (n=375)	**Recommended Phase 2 dosing:** Talquetamab 0.4 mg/kg SC qweek **OR** Talquetamab 0.8 mg/kg SC q2weeks	***0.4 mg/kg q week:*** **ORR:** 74% **VGPR:** 59% **CR:** 33% ***0.8 mg/kg q2weeks:*** **ORR:** 69% **VGPR:** 59% **CR:** 40%	**Median PFS 0.4 mg/kg q week:** 7.5 months **0.8 mg/kg q2weeks:** 11.2 months	***12-month OS 0.4 mg/kg q week:*** 76% ***0.8 mg/kg q2weeks:*** 77%	***CRS:*** **all-grade:** 76% **grade 3-4:** 1.5% ***ICANS:*** **all-grade:** 8% **grade 3-4:** 2% ***Infection:*** **all-grade:** 64% **grade 3-4:** 19% ***Dysgeusia:*** **all-grade:** 72% ***Rash:*** **all-grade:** 35% **grade 3-4:** 3.5% ***Non-rash skin toxicity:*** **all-grade:** 65% **Grade 3-4:** 0.3% ***Nail-related:*** **all-grade:** 55.5 ***Weight loss:*** **all-grade:** 40% **grade 3-4:** 3%
BOSTON[26]	Phase 3, randomized, open-label	Relapsed MM, 1-3 prior lines of therapy	**Standard Arm: Vd** Bortezomib 1.3 mg/m^2 SC d.1,4,8,11/21-day cycle, cycles 1-8; 1.3 mg/m^2 SC d. 1,8,15,22/35-day cycle, cycle 9 onward, until progression Dexamethasone 20 mg PO day of/ after bortezomib, until progression **Experimental Arm: SVd** Selinexor 100 mg PO, d. 1,8,15,22,29/35-day cycle, until progression Bortezomib 1.3 mg/m^2 SC, d. 1,8,15,22/35-day cycle, until progression Dexamethasone 20 mg PO, day of/ after each bortezomib dose, until progression	***SVd vs. Vd*** **ORR:** 76 vs. 62% **VGPR:** 45 vs. 32% **CR:** 17 vs. 10%	***Median PFS:*** **SVd:** 13.9 months **Vd:** 9.5 months (HR: 0.7, p=0.0075)	***Median OS*** **SVd:** NR **Vd:**25 months (HR: 0.84, p=NS)	***Thrombocytopenia:*** **grade 3-4:** **SVd:** 39% **Vd:** 17% ***Neutropenia:*** **grade 3-4:** **SVd:** 9% **Vd:** #% ***Fatigue:*** **all-grade/grade 3–4:** **SVd:** 42/18% **Vd:** 13/1% ***Nausea:*** **all-grade/grade 3–4:** **SVd:** 50/10% **Vd:** 8/0% ***Diarrhea:*** **all-grade/grade 3–4:** **SVd:** 32/25% **Vd:** 6/1% ***Weight loss:*** **all-grade/grade 3–4:** **SVd:** 26/12% **Vd:** 2/1%

Table 1. Pivotal trials (belantamab mafodotin, talquetamab, selinexor); *courtesy of Jesse Shustik, MD, FRCPC.*

Abbreviations: BPd: belamaf, pomalidomide, dexamethasone; **BVd:** belamaf, bortezomib, dexamethasone; **CR:** complete response; **CRS:** cytokine release syndrome; **DVd:** daratumumab, bortezomib, dexamethasone; **HR:** hazard ratio; **ICANS:** immune cell-associated neurologic syndrome; **IMID:** immunomodulatory drug; **IV:** intravenous; **MM:** multiple myeloma; **MRD:** minimal residual disease; **NR:** not reached; **NS:** not significant; **ORR:** overall response rate; **OS:** overall survival; **PFS:** progression-free survival; **PVd:** pomalidomide, bortezomib, dexamethasone; **SC:** subcutaneous; **SVd:** selinexor, bortezomib, dexamethasone; **Vd:** bortezomib, dexamethasone; **VGPR:** very good partial response.

	DREAMM-7[8,14]	DREAMM-8[9,14]
Standard belamaf schedule	2.5 mg/kg IV q3 weeks	2.5 mg/kg IV cycle 1, then 1.9 mg/kg IV q4 weeks (cycle 2 onward)
Dose modification (reduced dose level 1)	1.9 mg/kg IV q3 weeks	1.9 mg/kg IV q8 weeks
Grade ≥2 OEF incidence	86%	87%
Median time to onset, first grade ≥2 OEF	6 weeks	5 weeks
Resolution rate, first grade ≥2 OEF	81%	86%
Time to resolution, first grade ≥2 OEF	12 weeks	16 weeks
Visual acuity reduction 20/50, incidence	34%	34%
Visual acuity reduction 20/200, incidence	2%	1%
Resolution rate, visual acuity reduction to 20/50	94%	84%
Time to resolution, visual acuity reduction 20/50	9 weeks	8 weeks
Proportion of time on study with visual acuity <20/50	11%	14%
Ocular toxicity leading to dose delay, incidence	78%	75%
Ocular toxicity leading to dose reduction, incidence	44%	57%
Ocular toxicity leading to discontinuation, incidence	9%	9%

Table 2. Belantamab-related ocular toxicity, DREAMM-7/8 studies.[8,9,15]

Abbreviations: IV: intravenous; **OEFs:** ophthalmic examination findings

toxicity (**Table 3**).[13] Multidisciplinary collaboration between treating physicians and eye care professionals remains an essential component of therapy, and should include shared education strategies, efficient communication pathways, and clear reporting templates for ophthalmic exam findings. Serial ophthalmological evaluation remains obligatory during early cycles of therapy. However, in patients without ongoing toxicity, a vision-related patient questionnaire incorporating ocular symptoms and effects on activities of daily living has been proposed as a screening tool for treating clinicians, eliminating the need for regular eye care specialist assessment in patients without symptoms. In a preliminary evaluation in patients treated in a prospective belamaf trial, patients

	Examination findings per KVA scale	Recommended dose modifications
Grade 1	**Corneal examination finding(s)** • Mild superficial punctate keratopathy[a] **Change in BCVA[b]** • Decline from baseline of one line on Snellen Visual Acuity	• Continue according to belamaf prescribing information • Ophthalmic evaluation may be planned to confirm ocular event(s) do not worsen
Grade 2	**Corneal examination finding(s)** • Moderate superficial punctate keratopathy[c] **Change in BCVA[b]** • Decline from baseline of two or three lines (and Snellen Visual Acuity not worse than 20/200)	• Use Q8W dosing and maintain at new dose interval, provided recovery to Grade 1 • If ocular events remain Grade 2 after 8 weeks **OR** Grade 2 ocular events recur after initial recovery to Grade 1, consider extending dose interval to 12 weeks • If dose interval exceeds 12 weeks, reduce belamaf dosee
Grade 3	**Corneal examination finding(s)** • Severe superficial punctate keratopathy[d] **Change in BCVA[b]** • Decline from baseline by more than three lines (and Snellen Visual Acuity not worse than 20/200)	• Reduce belamaf dose[e] AND extend dose interval to at least 12 weeks and maintain at new dose interval, provided recovery to Grade 1 • If dose interval exceeds 16 weeks, further reduce belamaf dosee
Grade 4	**Corneal examination finding(s)** • Corneal epithelial defect **Change in BCVA[b]** • Snellen Visual Acuity worse than 20/200	• Consider treatment hold until Grade 1 • If continuing treatment with belamaf is being considered, reduce belamaf dose[e] AND extend dose interval to at least 12 weeks and maintain at new dose interval

Table 3. Recommended belamaf dose modifications following ocular events as defined by the KVA scale; *adapted from Terpos et al., 2024.*

[a] Mild superficial punctate keratopathy (documented worsening from baseline), with or without symptoms.
[b] Changes in visual acuity due to treatment-related corneal findings.
[c] Moderate superficial punctate keratopathy with or without patchy microcyst-like deposits, peripheral sub-epithelial haze (peripheral), or a new peripheral stromal opacity.
[d] Severe superficial punctate keratopathy with or without diffuse microcyst-like deposits involving the central cornea, sub-epithelial haze (central), or a new central stromal opacity.
[e] There are limited data on the efficacy of belamaf at doses lower than 1.9 mg/kg; if possible, the administration of doses below 1.9 mg/kg should be avoided.

Abbreviations: BCVA: best corrected visual acuity; **belamaf:** belantamab mafodotin; **KVA:** Keratopathy and Visual Acuity; **Q8W:** every 8 weeks.

monitored with a vision-related anamnestic tool exhibited no difference in rates of high-grade ocular toxicity compared to patients undergoing regular ophthalmological examination.[15] In the current Health Canada product monograph, ophthalmological examination is mandatory prior to each dose for the first 6 cycles of belamaf therapy, but may be reduced thereafter to every 3 months and whenever clinically indicated in patients without corneal or vision changes through the first 6 cycles.[16]

For prevention of ocular toxicity and management of low-grade symptoms, regular use of preservative-free lubricating drops and avoidance of contact lenses from the time of treatment initiation is advised. For grade ≥2

ophthalmic changes, current guidelines recommend dose delay until resolution and subsequent extension of the dosing interval to 8–12 weeks.[13] The use of more extended (8–12-week) belamaf dosing intervals as initial therapy has also been explored in recent combination studies and may become standard of care in the future.[12,17]

Talquetamab

Talquetamab is a first-in-class, humanized IgG4 bispecific antibody with binding to the CD3 receptor on T cells and to GPRC5D, an orphan transmembrane receptor with high levels of expression on malignant plasma cells but limited expression on normal plasma cells and other human tissues.[18] GPRC5D is highly expressed in the bone marrow of patients with myeloma and has been associated with high-risk disease features and adverse clinical outcomes. GPRC5D expression in normal tissues has been evaluated using sensitive analytic techniques, and in addition to plasma cells has been found in keratinized structures, including hair follicles, eccrine glands, and tongue.

In the first-in-human, phase 1–2 MonumenTAL-1 study, talquetamab was evaluated in a relapsed myeloma population with extensive previous treatment exposure, with a median of 6 prior lines of therapy, and 75% of patients triple-class-refractory to IMIDs, proteasome inhibitors, and anti-CD38 monoclonal antibodies.[19] In an updated analysis of patients treated at the recommended phase 2 doses (0.4 mg/kg subcutaneously weekly and 0.8 mg/kg subcutaneously every 2 weeks), the overall response rates (ORR) were 74% and 69% for the respective doses, with the majority of responders achieving VGPR or better, and similar rates were observed in a separate cohort of patients previously treated with anti-BCMA T-cell redirecting therapy.[20] Notably, the frequency of infectious complications and use of immunoglobulin replacement therapy was lower than that reported with anti-BCMA bispecific antibodies.

Toxicities associated with talquetamab include immunological events shared with other T cell-redirecting therapies (e.g., cytokine release syndrome [CRS], immune cell-associated neurologic syndrome [ICANS]), and unique 'on-target, off-tumour' toxicities likely related to GPRC5D expression on epithelial structures. Management of CRS/ICANS associated with talquetamab follows standard guidelines for T cell-redirecting therapies. Epithelial toxicities include oral, cutaneous, and nail effects; the incidence and temporal pattern of these toxicities are described in **Figure 1**. These are typically low-grade and rarely lead to treatment discontinuation, but may impact quality of life and require close management to ensure treatment adherence.[18,21]

Oral toxicity, including dysgeusia, dry mouth, and dysphagia, is commonly observed with talquetamab, with taste-related changes reported in approximately 75% of patients in the MonumentTAL-1 study.[20] The mechanism of dysgeusia as an on-target effect of talquetamab remains unclear, as GPRC5D expression on the tongue is limited to filiform papillae, which are not responsible for taste.[21] Taste changes typically develop within 1–2 months of initiation of therapy, are often persistent, and may be accompanied by clinically significant weight loss, occurring in approximately 40% of patients.[21] Various supportive therapies have been employed for dysgeusia, including steroid mouth rinses, zinc and biotin supplements, and salivary substitutes, though with limited evidence for efficacy. Talquetamab dose modifications have been suggested as the most effective mitigation strategy for oral toxicity.[18,21] Patients should be evaluated for oral comorbidities, including oral candidiasis, periodontal disease, and vitamin deficiencies leading to glossitis, and nutritional support may be required to minimize weight loss. In the MonumenTAL-1 study, weight loss was evident early, but with an overall stabilization or slight improvement over time, and cases of grade >3 weight loss (defined as >20% decrease from baseline weight) were rare.[20]

Cutaneous adverse events associated with talquetamab include skin rashes and "non-rash" skin toxicities, such as dry skin, pruritus, and skin exfoliation, most commonly affecting palms and soles.[21-22] Non-rash skin toxicities are more frequent, occurring in approximately two-thirds of patients, and require prophylactic or early use of emollients (e.g., ammonium lactate 12% or urea 10% cream) and sunscreen use for patients with photosensitivity. Skin rashes typically occur within the first month of therapy and resolve in most cases with the use of antihistamines, low-medium-potency topical corticosteroids, or short courses of oral corticosteroids for more extensive rashes. For persistent rashes,

Oral AEs	**Dysgeusia[1]** Incidence: 72.3% Grade 3/4: N/A Time to onset: 13–20 days Resolved: 38.3% Discontinuation: 0.6%	**Dysphagia** Incidence: 24.2% Grade 3/4: 0.9% Time to onset: 21–29 days Resolved: 65.9% Discontinuation: 0%	**Dry mouth** Incidence: 36.0% Grade 3/4: 0% Time to onset: 19–26 days Resolved: 39.0% Discontinuation: 0%
Skin and nail-related AEs (rash and no rash)	**Skin Rash[4]** Incidence: 34.8% Grade 3/4: 3.5% Time to onset: 20-27 days Resolved: 78.9% Discontinuation: 0%	**Skin Non-rash[6]** Incidence: 65.2% Grade 3/4: 0.3% Time to onset: 26-30 days Resolved: 59.4% Discontinuation: 0.9%	**Nail-related AEs[5]** Incidence: 55.5% Grade 3/4: 0% Time to onset: 64-69 days Resolved: 29.5% Discontinuation: 0%
Weight decrease Incidence: 39.5%[2] Grade 3/4: 3.2% Time to onset: 87-91 days[3] Resolved: 38.7% Discontinuation: 0.9%			

Figure 1. Summary of key AEs associated with talquetamab; *adapted from Chari et al, 2024; http://creativecommons.org/licenses/by/4.0/*

[1]Includes dysgeusia, ageusia, hypogeusia, and general taste disorders.
[2]The number of patients with a ≥ 10% decrease in weight from baseline in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts was 37.1%, 32.4%, and 29.4%, respectively.
[3]Time to onset for weight loss is reported for patients with a ≥ 10% decrease in weight from baseline.
[4]Includes rash, maculopapular rash, erythematous rash, and erythema.
[5]Includes nail discoloration, nail disorder, onycholysis, onychomadesis, onychoclasis, nail dystrophy, nail toxicity, and nail ridging.
[6]Includes skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome

Abbreviations: AE: adverse event; **CRS:** cytokine release syndrome; **ICANS:** immune effector cell-associated neurotoxicity syndrome; **QW:** weekly; **Q2W:** every other week.

a dermatology referral for consideration of skin biopsy may be warranted. Nail-related changes occur in 50–60% of patients and commonly persist for the duration of therapy, though rarely lead to dose modification or discontinuation.

Overall, dose modifications were infrequent for oral (7% of patients), skin (5%), and nail (1%) toxicities in the MonumenTAL-1 study, and treatment discontinuation occurred in only 2% of patients collectively for oral and dermatological toxicity.[20-21] However, despite supportive therapies described above, reductions in talquetamab dose or treatment frequency have been suggested as the most effective measure to ensure long-term treatment tolerability in patients with significant oral or cutaneous adverse events.[21] In a MonumenTAL-1 sub cohort, patients achieving at least a partial response prospectively underwent a reduction in talquetamab dose or extended treatment interval; despite dose reductions, all patients maintained responses, with a trend toward reduction in skin and oral toxicities.[23] The development of more refined toxicity grading systems and rational dose modification strategies is currently considered an area of high priority.[18,21]

Selinexor

Selinexor is an oral, first-in-class selective inhibitor of nuclear export with established activity in multiple myeloma. Its mechanism of action is based on inhibition of exportin 1 (XPO1), a nuclear export protein responsible for the traffic of over 200 "cargo proteins" from the cell nucleus to cytoplasm, leading to retention of tumour suppressor proteins in the nucleus and blockade of oncoprotein mRNA transfer to the cytoplasm.[24] Although initial use was based on studies demonstrating ORRs of 25–30% (in combination with dexamethasone alone) in heavily-pretreated patient populations, subsequent development of selinexor has focused on multidrug combination therapy with use in earlier treatment lines.[24-25] In the phase 3 BOSTON trial, weekly selinexor in combination with bortezomib-dexamethasone (SVd) demonstrated statistically higher ORR (76% vs. 62%), ≥VGPR (45 vs. 32%), and median PFS (13 vs. 9.5 months; HR: 0.7; p=0.0075) in comparison with a standard therapy arm of twice-weekly bortezomib-dexamethasone (Vd), in patients with relapsed multiple myeloma after 1–3 prior lines of therapy.[26] Current Health Canada approval of selinexor is for use in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Selinexor has a distinct toxicity profile that includes hematological (thrombocytopenia, neutropenia), gastrointestinal (nausea, diarrhea), and constitutional adverse effects (fatigue, anorexia, weight loss), leading to high rates of early treatment discontinuation in initial studies.[24-25] While these studies employed a more intensive twice-weekly dosing schedule, the use of weekly selinexor dosing was evaluated in subsequent multiagent combination regimens, leading to a chosen selinexor dose of 100 mg weekly in the phase 3 BOSTON study. By consensus, weekly selinexor dosing has reduced the severity of adverse effects,[27] though previous toxicities are still commonly observed. In the BOSTON study, toxicities occurring with higher frequency in the SVd arm included thrombocytopenia (all-grade/grade 3–4: 60/39%), neutropenia (35/9%), nausea (50/8%), vomiting (30/4%), diarrhea (32/6%), fatigue (42/13%), anorexia (35/4%), and weight loss (26/2%).[26]

Aggressive supportive care and liberal dose reduction are the mainstays of selinexor toxicity management, and physician comfort with both strategies is likely to be associated with improved treatment adherence and outcomes.[27-28] Key supportive measures are described below. Although the starting selinexor dose in the BOSTON study was 100 mg weekly, the majority of patients in the SVd arm (65%) required dose reduction, leading to an actual median selinexor dose of 80 mg weekly in this study. In a post-hoc analysis, patients treated with SVd undergoing selinexor dose reduction had improved outcomes in comparison with those who did not (median PFS: 16.6 vs. 9.2 months).[29] In clinical practice, lower weekly doses of selinexor (i.e., 40–80 mg weekly) are commonly effective, and may be justified as initial therapy in the majority of patients. Notably, more recent combination studies with pomalidomide or carfilzomib backbones have employed selinexor doses ranging from 40–80 mg weekly, with promising efficacy.[30-31]

Thrombocytopenia represents the most common hematological toxicity associated with selinexor and has been attributed to inhibition of thrombopoietin signalling during early megakaryopoiesis. The kinetics of selinexor-associated thrombocytopenia are unique, typically occurring 2–3 weeks after treatment, resulting in an approximately 50% reduction in platelet counts, and resolving within 1–2 weeks after drug interruption.[24,27] The use of thrombopoietin agonists or platelet transfusions was required in approximately one-quarter of patients in the BOSTON study, but clinically significant bleeding events were rare.[26] Current guidelines recommend dose reduction for patients with platelet counts of <50,000 and treatment interruption for patients with platelet counts of <25,000, though additional caution may be required in patients with additional bleeding risks, such as concurrent anticoagulant use.[27]

Selinexor-associated nausea is believed to relate to central nervous system effects from drug passage across the blood-brain barrier and requires aggressive antiemetic prophylaxis during initiation of therapy. Routine prophylaxis with an NK-1 inhibitor in addition to a 5-HT3 antagonist (e.g., aprepitant plus ondansetron, netupitant-palonosetron) should now be considered standard; in patients with ongoing nausea or restricted access to NK-1 inhibitors, prophylaxis with olanzapine (2.5–5 mg in the evening for 1–3 days after selinexor) may also be used.[27] The incidence of nausea decreases significantly after the first two months of therapy, and may allow tapering of the antiemetic regimen.

Other frequent nonhematological toxicities include anorexia and fatigue, which may be high-grade in nature. Reduction in oral intake may be associated with weight loss and dehydration, and close nutritional monitoring with high-caloric supplementation and maintenance of adequate oral fluid intake (at least 2L daily) are advised.[27] Hyponatremia occurs frequently and requires close laboratory monitoring during initial cycles, with correction by sodium chloride tablets if present. Fatigue may respond to nutritional optimization and treatment of gastrointestinal toxicities, but for persistent fatigue, the use of methylphenidate has had reported benefit.

Conclusion

Belantamab mafodotin, talquetamab, and selinexor are novel targeted therapies with proven activity in relapsed multiple myeloma and represent attractive treatment options in patients with relapse after treatment with IMIDs, proteasome inhibitors, and/or anti-CD38 monoclonal antibodies. Although these agents are associated with distinct adverse effect profiles, discontinuation due to toxicity is only required in a minority of patients, and further dose optimization after initial approval and increased clinician experience with use are also likely to improve treatment delivery and outcomes. The use of these agents may further evolve as new drug combinations, use in earlier lines of therapy, and fixed-duration approaches are explored.

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