International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma

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Multiple myeloma remains an incurable disease, despite the development of numerous drug classes and combinations that have contributed to improved overall survival. Immunotherapies directed against cancer cell-surface antigens, such as chimeric antigen receptor (CAR) T-cell therapy and T-cell-redirecting bispecific antibodies, have recently received regulatory approvals and shown unprecedented efficacy. However, these immunotherapies have unique mechanisms of action and toxicities that are different to previous treatments for myeloma, so experiences from clinical trials and early access programmes are essential for providing specific recommendations for management of patients, especially as these agents become available across many parts of the world. Here, we provide expert consensus clinical practice guidelines for the use of bispecific antibodies for the treatment of myeloma. The International Myeloma Working Group is also involved in the collection of prospective real-time data of patients treated with such immunotherapies, with the aim of learning continuously and adapting clinical practices to optimise the management of patients receiving immunotherapies.

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Introduction

In the past two decades, considerable advances in the treatment of multiple myeloma have led to improved survival rates. However, patients who become refractory to proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies have dismal outcomes, with a median overall survival of around 1 year,[1] underscoring the need for new treatments for patients with relapsed or refractory multiple myeloma.[1,2] Several promising drugs with novel mechanisms of action have been approved for relapsed or refractory multiple myeloma within the past 2 years, including chimeric antigen receptor (CAR) T-cells (ide-cel and cilta-cel) and T-cell-redirecting bispecific antibodies.

Bispecific antibodies are a class of immunotherapy designed to simultaneously bind to T cells via CD3 and to surface antigens on the tumour cell. This dual binding induces the redirection and activation of the T cells against the tumour, resulting in the release of granzymes and perforins as well as pro-inflammatory cytokines, leading to HLA-independent T-cell-mediated tumour cell killing.[3] Multiple bispecific antibodies are in development that target different antigens on multiple myeloma cells, with the most relevant tumour-associated antigens being BCMA, GPRC5d, and FcRH5.[4–6]

This Policy Review provides a consensus statement aiming to optimise care for patients receiving bispecific antibody therapy.

Data collection

A panel of 37 experts with broad experience in the management of patients with relapsed or refractory multiple myeloma was convened by the International Myeloma Working Group (IMWG). We reviewed articles with at least 50 patients enrolled (appendix pp 2–4), as well as two consensus papers.[7,8] Several virtual meetings were held from 2022 to 2023 to define optimal management strategies. To provide consensus recommendations about infectious complications, an electronic questionnaire was developed, and 50 experts participating in the IMWG Immunotherapy Subcommittee were asked to give their vote and feedback. Statements with a high agreement (>50%) were incorporated as recommendations (appendix pp 9–11). This Policy Review summarises the panel's consensus and provides recommendations for management of bispecific antibodies for the treatment of relapsed or refractory multiple myeloma.

Summary of efficacy and safety data for drugs with more advanced development

To date, three bispecific antibodies have received accelerated regulatory approvals and many others are in development. A summary of key efficacy and safety data of several bispecific antibodies approved or in development is included in table 1.[5,6,9–15]

Teclistamab

Teclistamab is a BCMA-CD3 bispecific antibody that was first approved by the European Medicines Agency (EMA) in August, 2022, for the treatment of patients who have previously received three or more therapies and then by the US Food and Drug Administration (FDA) in

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	Target	Route	Dose and schedule	Number of participants	Median number of previous lines of treatment (range)	Triple refractory, n (%)	Cytokine release syndrome; grade ≥3, n (%)	Neurotoxicity; grade ≥3, n (%)	Infections; grade ≥3, n (%)	Overall response, n (%)	Complete response or better, n (%)	Median progression-free survival, months (95% CI)	Median duration of response, months (95% CI)	Minimal residual disease (10^{-5}) negative, n/N (%)
Teclistamab[5]*	BCMA-CD3	Subcutaneous	1·5 mg/kg weekly	165	5 (2–14)	128 (77·6%)	119/165 (72·1%); 1/165 (0·6%)	5/165 (3%); 0	126/165 (76·4%); 74/165 (44·8%)	104/165 (63%)	65/165 (39·4%)	11·3 (8·8–17·1)	18·4 (14·9–NE)	44/165 (26·7%)
Linvoseltamab[15]	BCMA-CD3	Intravenous	200 mg weekly for 16 weeks; week ≥16: every 2 weeks	221	50 mg: 6 (3–14); 200 mg: 5 (2–14)	50 mg: 91 (87·5%); 200 mg: 86 (73·5)%	53/117 (45·3%); 1/117 (0·9%)†	7/117 (5·9%); 2/117 (1·7%)	70/117 (59·8%); 43/117 (36·8%)†	83/117 (71%)†	35/117 (30%)	Not reached at 6 months (72·7%)	Not reached	25/46 (54·3%)
ABBV-383[11]	BCMA-CD3	Intravenous	Every 3 weeks	124	5 (1–15)	102 (82%)	71 (57%); 3 (2%)	6 (5%)	51 (41%); 31 (25%)	69 (57%)‡	35 (28%)§	10·4 months (range 5·0–19·2)	Not reported	Not reported
Elranatamab[13,14]*	BCMA-CD3	Subcutaneous	76 mg weekly; ≥7 cycles: every 2 weeks if partial response	123	5 (2–12)	119 (96%)	71 (57·7%); 0	5 (4%); 4 (3%)	82 (67%); 43 (35%)	75 (61%)	46 (37·4%)	17·2 (9·8–NE)	NE (12·0–NE)	27/30 (90%)
Alnuctamab[12]	BCMA-CD3 (2+1 binding)	Subcutaneous	30 mg weekly for 8 weeks; every 2 weeks for cycles 3–7; every 4 weeks for ≥7 cycles	78	4 (3–11)	43 (63%)	36 (53%); 0%	2 (3%); 0%	23 (34%); 6 (9%)	39 (53%)	17 (23%)	Not reported	Not reported	16/20 (80%)
Talquetamab[6]*	GPRC5d-CD3	Subcutaneous	0·4 mg/kg weekly	143	5 (2–13)	106 (74·1%)	113/143 (79%); 3 (2%)	19 (13·9%); 1 (1·6%)	82 (57·3%); 24 (16·8%)	106 (74·1%)	48 (33·6%)	7·5 (5·7–9·4)	9·3 (6·6–12·7)	Not reported
Talquetamab[6]*	GPRC5d-CD3	Subcutaneous	0·8 mg/kg every 2 weeks	145	5 (2–17)	100 (69%)	105/145 (72·4%); 1 (0·7%)	14 (10%); 3 (2%)	73 (50·3%); 17 (11·7%)	106 (73·1%)	47 (32·4%)	11·9 (8·4-NE)	13·0 (10·6–NE)	Not reported
Forimtamig[10]	GPRC5d-CD3 (2+1 binding)	Subcutaneous	1200–7200 µg/kg; every 2 weeks	57	4 (2–14)	40 (71·9%)	43 (78·9%); 1 (1·8%)	7 (12·3%); 3 (0·6%)	26 (45·6%); 15 (26·4%)	35 (63·6%)	14 (25·5%)	Not reported	12·5 (1·2–12·5)	10/14 (71%)
Cevostamab[9]	FcRH5-CD3	Intravenous	Every 3 weeks	157	6 (2–18)	133 (85%)	127 (81%); 2 (1%)	22 (14·3%); 1 (0·6%)	71 (45%); ND	34 (56·7%); 60 patients treated at 132–198 mg	5 (8·4%)	Not reported	11·5 (6–18·4)	7/10 (70%)

ND=not determined. NE=not estimable. *Commercially available. †At the recommended phase 2 dose (200 mg). 54 (68%) of 79 patients treated at ≥40 mg in the dose escalation and expansion phase. §12 (20%) of 60 patients treated at ≥40 mg in the dose escalation and expansion phase.

Table 1: **Summary of key efficacy and safety data of main bispecific antibodies in development**

October, 2022, for patients who have previously received four or more treatments.

Approval was based on the results of the phase 1 MajesTEC-1 study,[16] which enrolled 157 patients and identified the recommended phase 2 dose of teclistamab; 1·5 mg/kg given subcutaneously weekly following two step-up doses of 0·06 mg/kg and 0·3 mg/kg. The phase 2 expansion enrolled 165 patients.[5] The study reported grade 3 or 4 adverse events in 156 (94·5%) of 165 patients. The most notable adverse events related to T-cell redirection included cytokine release syndrome in 119 (72·1%) of 165 patients, neurological adverse events in 24 (14·5%) of 165 patients, and immune effector cell-associated neurological toxicity in five (3·0%) of 165 patients; almost all of these events were grade 1 or grade 2 and mostly occurred during the step-up and cycle 1 dosing (95% of cases), with comparable safety in recently reported real-world cohorts.[17–21] Haematological toxicity (>90%) and infection (126 [76·4%] of 165) were frequent, and 12 (7·3%) patients died from COVID-19.

Talquetamab

Talquetamab, a subcutaneous GPRC5d-CD3 bispecific antibody, was approved by the FDA and EMA in August, 2023. Accelerated approval was based on the results of the MonumenTAL-1 phase 1–2 study, which generated two recommended phase 2 dose dosing schedules (0·4 mg/kg subcutaneously once weekly and 0·8 mg/kg subcutaneously once every 2 weeks) and showed overall response rates (ORRs) of 74·1% (106 of 143 patients) with the 0·4 mg/kg dose and 73·1% (108 of 145 patients) with the 0·8 mg/kg dose; median progression-free survival was 7·5 months (95% CI 5·7–9·4) with the 0·4 mg/kg dose and 11·9 months (95% CI 8·4–NE) with the 0·8 mg/kg dose. The study reported serious adverse events in 135 (47%) of 288 patients, but very few patients discontinued therapy due to adverse events. Haematological toxicity was common, as well as several non-haematological adverse events (incidence >40%) including pyrexia (88 [33%] of 288), cytokine release syndrome (218 [76%] of 288), dysgeusia (136 [47%] of 288), infection (175 [61%] of 288), nail disorders (144 [50%] of 288), musculoskeletal pain (124 [43%] of 288), and skin disorders (118 [41%] of 288).[6]

Elranatamab

Elranatamab was approved by the FDA and EMA in August, 2023, and is the second approved BCMA-CD3 bispecific antibody. It was approved on the basis of the results of the MagnetisMM-3 Study, involving 123 patients with relapsed or refractory multiple myeloma, and showed an ORR of 61% (95% CI 52–70; 75 of 123 patients), with the median duration of response not reached (95% CI 12–NE) and a median progression-free survival of 17·2 months (95% CI 9·8–NE).[13,14] This bispecific antibody was given subcutaneously weekly at a fixed dose of 76 mg with two step-up doses (12 mg and 32 mg), and responders at 24 weeks decreased the frequency of dosing to every 2 weeks. Similar safety signals to other BCMA-targeting bispecific antibodies have been noted, including a high incidence of haematological toxicity (>80%), cytokine release syndrome (71 [58%] of 123), and infection (82 [67%] 123, grade 3–4 in 43 [35%] of 123).[13,14]

Toxicity and management

Cytokine release syndrome

Cytokine release syndrome is a systemic inflammatory reaction resulting from bispecific antibody-mediated T-cell activation, leading to secretion of pro-inflammatory cytokines such as IL-2, IL-6, IFN-γ, and TNF.[22–26] The clinical presentation varies from isolated fever to, if not properly recognised and timely treated, severe reactions, including hypotension, tachypnoea, and hypoxaemia. All bispecific antibodies currently in clinical development for multiple myeloma induce cytokine release syndrome, which is mostly grade 1 or 2, and generally confined to the step-up doses or first full dose (table 2).[5,9–12,16,25,27–29] The differences reported in the frequency of cytokine release syndrome between the different bispecific antibodies can be partly explained by the variability in the number of step-up doses, use and schedule of pre-medications, route of administration, and differences in CD3-binding affinity.[11] The median time to onset of cytokine release syndrome is within 24 h of intravenous infusion of bispecific antibodies, whereas it occurs after at least 24 h with subcutaneous administration, which can be explained by the gradual increase in serum concentration with subcutaneous administration.[16]

Diagnostic investigation of cytokine release syndrome

The occurrence of cytokine release syndrome is highly predictable. Different mitigation strategies are implemented to decrease the incidence and severity of

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See **Online** for appendix

	All grade, n/N (%)	Grade 3 or higher, n/N (%)	Median time (range) to onset, any grade	Median duration (range), any grade
BCMA–CD3-targeted				
Teclistamab[5]	119/165 (72·1%)	1/165 (0·6%)	2 days (1–6)	2 days (1–9)
Elranatamab[13,14]	71/123 (57·7%)	0/123 (0%)	2 days (1–9)	2 days (1–19)
Linvoseltamab[15] (200 mg)	51/117 (44%)	1/117 (0·9%)	14·8 h (0–177)	16·5 h (1–144)
ABBV-383[11] (≥40 mg)	71/124 (72·8%)	0/124 (0%)	1 day (1–7)	1 day (1–8)
Alnuctamab[12]	43/78 (55%)	0/78 (0%)	3 days (1–20)	2·5 days (2–10)
GPRC5D–CD3-targeted				
Talquetamab[6] (405 μg/kg)	113/143 (79%)	3/143 (2·1%)	2 days (1–8)	2 days (1–13)
Talquetamab[6] (800 μg/kg)	105/145 (72·4%)	1/45 (0·7%)	2 days (1–8)	2 days (1–29)
Forimtamig[10]	45/57 (78·4%)	1/57 (2·0%)	5 h	2 days
FCRH5–CD3-targeted				
Cevostamab[9]	130/161 (80·7%)	2/161 (1·2%)	NR; onset within 24 h in 113/161 (70%)	NR; resolution within 48 h in 137/161 (85%)

NR=not reported.

Table 2: **Cytokine release syndrome with bispecific antibodies**

cytokine release syndrome, such as step-up doses and premedication. However, because the signs and symptoms overlap with those of infections or other disorders, a detailed medical history, physical examination, and laboratory investigations should be performed in all suspected cases. Complete blood counts and comprehensive metabolic panels, including inflammatory markers and coagulation tests, are highly recommended. A full infectious investigation including blood culture, urine culture, urine analysis, and chest x-ray should be considered on the basis of clinical findings. C-reactive protein concentrations are not useful for monitoring after the use of tocilizumab, because C-reactive protein is induced by the IL-6 pathway and its concentration tends to decrease after tocilizumab usage. However, procalcitonin might be of value in this setting. The use of broad-spectrum antibiotics should be considered especially if neutropenia co-exists. In general, bispecific antibodies should not be administered during an active infection, because infections might precipitate severe cytokine release syndrome.[5,6,25] Additionally, if bispecific antibody therapy has been interrupted for a considerable period of time (generally >4 weeks), repeating the step-up dosing should be considered when resuming treatment to avoid inducing cytokine release syndrome.

Grading and management of cytokine release syndrome

There are multiple grading scales for cytokine release syndrome, but to improve uniformity across studies we recommend using the consensus grading guidelines from the American Society for Transplantation and Cellular Therapy (appendix p 3),[30] which consider temperature, blood pressure, and oxygen saturation.

***Panel 1*: Management of cytokine release syndrome**

Grade 1: observation
- Consider early tocilizumab use
- If persistent grade 1 (>24–48 h), early use of tocilizumab is encouraged

Grade 2: tocilizumab 8 mg/kg intravenously
- If no improvement, consider adding second line treatment (ie, steroids)
- Supportive care including oxygen supplementation, fluids, should be implemented

Grade 3: tocilizumab plus dexamethasone 10 mg every 6 h
- Transfer the patient to ICU
- Supportive care as clinically indicated
- Consider high-dose steroids and salvage CRS treatment (ie, anakinra)

Grade 4: tocilizumab plus high-dose steroids
- Transfer the patient to ICU
- Supportive care as clinically indicated
- Consider high-dose steroids and salvage CRS treatment (ie, anakinra)

ICU=intensive care unit. CRS=cytokine release syndrome.

Patients should be monitored during bispecific antibody therapy for signs and symptoms of cytokine release syndrome, such as fever, to allow for early intervention. Treatment of cytokine release syndrome should take into consideration the individual agent and be guided by the available data. The goals of management should be to prevent or minimise any or all symptoms of cytokine release syndrome. As such, prophylactic use of tocilizumab, an IL-6 receptor-blocking antibody, has been evaluated in several trials. In a study of cevostamab, a bispecific antibody targeting FcRH5 and CD3, 31 patients received tocilizumab 2 h before the initial step-up dose. The incidence and severity of cytokine release syndrome in these patients were compared with the incidence and severity reported in 44 patients treated with cevostamab without tocilizumab. Prophylactic tocilizumab (8 mg/kg) efficiently reduced the overall incidence of cytokine release syndrome from 90·9% (40 of 44 patients) to 38·7% (12 of 31 patients), with no negative impact on disease response, although the incidence of grade 3–4 neutropenia was higher.[31] In a study of teclistamab, 23 patients received tocilizumab prophylaxis within 4 h of step-up dosing. Compared with patients treated in the MajesTEC-1 study with standard prophylaxis without tocilizumab, a single dose of tocilizumab efficiently reduced the overall incidence of cytokine release syndrome from 72·1% (119 of 165 patients) to 26·1% (six of 23 patients), with the greatest benefit in preventing grade 1 events as the rates of grade 2 events appeared to be similar to those reported in MajesTEC-1 (21·2% [35 of 165 patients] *vs* 17·4% [four of 23 patients]).[32] Prophylactic use of tocilizumab is currently considered investigational and not recommended outside of a clinical trial, although the evidence of its use in the real-world setting is progressively increasing.[33,34]

In patients who develop cytokine release syndrome, supportive care should be initiated, including prompt administration of acetaminophen, intravenous fluids, and oxygen as needed. Panel consensus supports early administration of tocilizumab in patients with grade 1 cytokine release syndrome, even at the first sign of fever, because tocilizumab is rapidly effective and prevents progression of severity, without evidence of a reduction in efficacy[22] (panel 1). Moreover, it is likely that early intervention prevents additional toxicity and shortens hospital stay.[35] In MajesTEC-1, tocilizumab use decreased the recurrence of cytokine release syndrome with subsequent dosing, further supporting this strategy.[35] Tocilizumab is given intravenously at a dose of 8 mg/kg (maximum dose 800 mg) and can be repeated, generally for a maximum of three doses in 24 h. If cytokine release syndrome persists or recurs after 1–3 doses of tocilizumab, second-line therapy can be started (ie,

steroids and anakinra, among others). Repeat dosing of tocilizumab was not needed in most cases of cytokine release syndrome in MajesTEC-1.

Alternatively, there was also support from a minority of panellists for monitoring without tocilizumab or aggressive intervention for initial grade 1 cytokine release syndrome, and for the use of steroids (eg, dexamethasone 10 mg) as first-line treatment and reserving tocilizumab (or other available drugs with a similar mode of action) for persistent or recurrent cytokine release syndrome unresponsive to steroids (panel 1). The evidence supporting initial management of multiple myeloma with steroids in the setting of bispecific antibodies is very scarce. The combination of tocilizumab and steroids is recommended for treatment of grade 3 or worse cytokine release syndrome, but these events are infrequent with bispecific antibodies in multiple myeloma.

Overall, patients typically recover quickly with standard supportive care,[30] but on rare occasions severe cytokine release syndrome might require intensive monitoring and support (eg, vasopressor administration, anakinra, and steroids), preferably in an intensive care unit setting with staff experienced in managing such patients. A summary of panel recommendations for management of cytokine release syndrome is included in the appendix (pp 9–11).

For the initial clinical trials with all bispecific antibodies, inpatient hospital monitoring during step-up or the first full dose, or both, was required. However, in the real-world setting, outpatient dosing is currently being explored at selected centres as well as tocilizumab prophylaxis.[18,19,33,34] Standard operating procedures should be developed to optimise local care for bispecific antibodies.

Neurological complications

Clinical presentation of neurological complications

The three main types of neurotoxicity that have been reported with bispecific antibodies are headache, immune effector cell-associated neurological toxicity, and peripheral neuropathy (panel 2 and appendix p 6), and reporting varies across trials. Headache has been reported as a non-specific neurotoxic event in most immunotherapy clinical trials, because it can be associated with cytokine release syndrome and often responds to treatment with acetaminophen or local measures (eg, local cold). Immune effector cell-associated neurological toxicity is less common but believed to be triggered by passive diffusion of cytokines and trafficking of T cells into the CNS, monocyte recruitment, and macrophage activation. It often happens concurrent to or following cytokine release syndrome and typically consists of varying degrees of diffuse encephalopathy with or without focal signs, intracranial hypertension, or seizures.[36,37] Peripheral neuropathies have been mostly sensory and are associated with a previous history of peripheral neuropathy.

***Panel 2*: Management of immune effector cell-associated neurotoxicity syndrome**

Grade 1 (ICE score 7–9): observe
- Can consider early dexamethasone in high-risk patients
- Consider non-sedating anti-epileptic drugs

Grade 2 (ICE score 3–6): dexamethasone 10 mg every 12 h
- If no improvement after 48 h, consider high dose dexamethasone (20 mg every 6 h) and alternative agents such as anakinra
- Start non-sedating anti-epileptic drugs
- Consider EEG and CT/MRI imaging

Grade 3 (ICE score 0–2): dexamethasone 10 mg every 6 h
- If no improvement after 24 h consider high dose dexamethasone (20 mg every 6 h), high dose methylprednisolone (1–2 g per day) and/or alternative agents such as anakinra
- Start non-sedating anti-epileptic drugs if not on already
- Perform CT/MRI imaging, consider EEG
- Consider CSF evaluation for other causes and pressure measurement
- Transfer the patient to ICU

Grade 4 (ICE score 0): dexamethasone 10 mg every 6 h
- In dexamethasone refractory patients, consider high dose methylprednisolone 2 mg/kg every 12 h
- For refractory patients consider alternative therapies (IL-1 blockers, such as anakinra)
- Start non-sedating anti-epileptic drugs if not on these already
- Perform CT/MRI imaging, consider EEG (if not previously done)
- Consider CSF evaluation for other causes and pressure measurement (if not previously done)
- Patient should be in the ICU

ICE=immune effector cell encephalopathy. EEG=electroencephalogram. ICU=intensive care unit.

Frequency of neurological complications in clinical trials

In MajesTEC-1, headache was reported in 14 (8·5%) of 165 patients, all of which were grade 1–2 events except for one patient with a grade 3–4 event. Immune effector cell-associated neurological toxicity was reported in five (3%) of 165 patients (table 1), all grade 1 or 2, and almost all cases were concurrent with cytokine release syndrome and all resolved without the need for treatment discontinuation or dose reduction. Peripheral sensory neuropathy related to teclistamab was only described in a single case (0·6%),[5] with other terms such as motor dysfunction reported in 26 (16%) of 165 patients and sensory neuropathy reported in 25 (15%) of 165 of patients.[38] In the MagnetisMM-3 trial, headache occurred in 29 (23·6%) of 123 patients, all grade 1 or 2 events.[28,39] Immune effector cell-associated neurological toxicity was reported in four (3·4%) of 123 patients, all grade 1 or 2

events. The median time to onset was 2·5 (range 1·0–4·0) days, with a median time to resolution of 2 (range 1·0–6·0) days. peripheral neuropathy was observed in 20 (16%) of 123 patients, all grades 1–2 except for one patient with grade 3 motor neuropathy. A previous medical history of peripheral neuropathy was observed in 58 (47%) of 123 patients.

A delayed parkinsonian syndrome unresponsive to levodopa has been reported in several patients following BCMA-targeted CAR-T cell therapy. It is hypothesised to be an on-target off-tumour effect of CAR-T cells on BCMA-expressing astrocytes and neurons in the basal ganglia, mainly in the caudate nucleus.[40] This neurotoxic event has not been reported with BCMA–CD3-targeted bispecific antibodies, although the follow-up duration is still rather short (9–24 months).

In the MonumenTAL-1 trial, headache, as a non-specific symptom, was reported in 28 (21·5%) of 130 patients, with only one (0·8%) of 130 patients reporting grade 3 events. Immune effector cell-associated neurological toxicity was reported in 13 (10·7%) of 122 patients treated with talquetamab 0·4 mg/kg once weekly and 11 (10·1%) of 109 patients treated with talquetamab 0·8 mg/kg once every 2 weeks, with two patients in each cohort having grade 3 immune effector cell-associated neurological toxicity.[41] Only one (0·8%) patient developed paresthesia.[6] Almost all neurotoxic events occurred during step-up doses and within cycle 1. In a dose-escalation study of forimtamig, a bispecific antibody targeting GRPC5D and CD3, immune effector cell-associated neurological toxicity occurred in seven (12·3%) of 57 patients, with two (3·6%) of 57 events being grade 3 or worse in the subcutaneous cohorts.[10]

In the phase 1 dose-escalation study of cevostamab, 23 (14·3%) of 161 patients developed immune effector cell-associated neurological toxicity, mostly grade 1 or 2, with only one (0·6%) of 161 patients developing grade 3 events. The most common symptoms related to immune effector cell-associated neurological toxicity were confusional state and aphasia.[9]

Evaluation and management of neurotoxicity

Specific scoring systems have been developed to assess the occurrence and severity of immune effector cell-associated neurological toxicity. The Immune Effector Cell-Associated Encephalopathy (ICE) score has been adopted by the American Society for Transplantation and Cellular Therapy for evaluation of immune effector cell-associated neurological toxicity, and results from a combined assessment of orientation, naming, following of commands, writing, and attention (appendix p 4). Grading of immune effector cell-associated neurological toxicity is then based on the total score from the following domains: ICE score, level of consciousness, seizures, motor findings, and signs of elevated intracranial pressure or cerebral oedema (appendix p 5).[30]

Baseline and at least twice-daily neurological and ICE examinations are performed during initiation of bispecific antibody therapy, but once neurotoxicity is suspected, more frequent serial neurological examinations with immune effector cell-associated neurological toxicity grading are performed. Additional diagnostic investigation requires the exclusion of other potential causes such as toxic, metabolic, or infectious encephalopathy, clinical or subclinical seizures, focal structural lesions, such as haemorrhagic or ischaemic stroke, and tumour progression within the CNS. For immune effector cell-associated neurological toxicity that is grade 2 or worse, an EEG should be performed to rule out non-convulsive seizures, and a CT or ideally MRI scan should be done to rule out cerebral oedema and other acute abnormalities. Lumbar puncture for cerebrospinal fluid analysis can be considered, especially if there is suspicion of CNS infection or tumour infiltration (appendix p 6).

Management of immune effector cell-associated neurological toxicity primarily relies on the use of corticosteroids, with dexamethasone being the preferred initial treatment (panel 2). For grade 1 immune effector cell-associated neurological toxicity, observation can generally be considered, except in high-risk patients such as older patients or those with a high tumour burden in whom early treatment with dexamethasone is encouraged to prevent progression. Dexamethasone should be started at 10 mg every 8–12 h for management of grade 2 immune effector cell-associated neurological toxicity. Patients with grade 3 or 4 immune effector cell-associated neurological toxicity should be monitored in the ICU and the dexamethasone dose can be increased to 10–20 mg every 6 h or patients can be switched to high-dose intravenous methylprednisolone (ie, 500 mg to 1 g every 24 h). Additionally, prophylaxis with non-sedating anti-epileptic drugs can be considered in any patient with neurotoxicity but especially in those with grade 3–4 toxicity. For persistent neurotoxicity, consider a neurology consultation and the use of alternative agents such as anakinra.[42] A summary of panel recommendations about the management of neurotoxicity are included in panel 2 and the appendix (pp 12–17).

Peripheral neuropathy can worsen on therapy and can be assessed by nerve conduction studies and electromyography. Treatment might require temporary interruption of bispecific antibodies or a short course of steroids can be prescribed in selected cases, notably in patients with a high suspicion of an immune-mediated underlying mechanism.

Haematological adverse events

Haematological adverse events or cytopenias are a function of disease refractoriness or toxicity of previous therapies, as well as a result of treatment-emergent adverse events related to both the BCMA-directed and non-BCMA-directed bispecific antibodies. Most studies of bispecific antibodies[5,6,10,11,27,28] have enrolled heavily

pretreated patients, suggesting a poor bone marrow reserve as a major contributing factor for cytopenias.

The temporal effect of cytopenias following the administration of T-cell bispecific antibodies and the count recovery following dose delays suggest that the cytopenias are also treatment related.[43] However, the exact mechanism and the underlying aetiology of cytopenias with bispecific antibodies are poorly understood. The cytokine storm or milieu associated with cytokine release syndrome probably contributes to bone marrow suppression but additional data are needed to better define this important form of toxicity.

Incidence and severity of cytopenias with T-cell-engaging bispecific antibodies

Cytopenias are commonly reported across all clinical trials of bispecific antibodies, including neutropenia (any grade 28·3–70·9%, grade ≥3 22·1–64·2%), anaemia (any grade 34·2–52·1%, grade ≥3 22·4–37%), thrombocytopenia (any grade 23·5–40%, grade ≥3 8·8–25·9%), and lymphopenia (any grade 16·1–34·5%, grade ≥3 16·1–32·7%). Haematological toxicities are the most common higher-grade (grade ≥3) toxicities seen in all trials.

The dynamics of cytopenias in relation to treatment are currently evolving, but cytopenias appear more common earlier in treatment and seem to be more common with the BCMA-targeting T-cell-engaging bispecific antibodies than with the non-BCMA-targeting agents. Talquetamab was evaluated in two dosing schedules, 0·4 mg/kg weekly and 0·8 mg/kg once every 2 weeks. Numerically, the incidence of grade 3 or worse neutropenia (44 [30·8%] of 143 with 0·4 mg/kg weekly *vs* 32 [22·1%] of 145 with 0·8 mg/kg once every 2 weeks), anaemia (45 [31·5%] of 143 *vs* 36 [24·8%] of 145), thrombocytopenia (29 [20·3%] of 143 *vs* 24 [16·6%] of 145) and lymphopenia (37 [25·9%] of 143 *vs* 37 [25·5%] of 145) is lower than that reported for BCMAs. However, data on late (>30 days) haematopoietic recovery are lacking and there might be an underestimation of the rates and the severity of cytopenias over time and relatedness to infection. In patients with persistent or unexplained cytopenias a complete evaluation should be done to rule out other possible causes (ie, iron deficiency, myelodysplasia, and so on).

Management

Most haematological toxicities can be easily managed with dose delays and supportive care strategies. Growth factor use has been generally allowed, although not during active cytokine release syndrome. A summary of recommended management is provided in table 3 and the appendix (pp 12–19).

	Frequency of visits	Management strategy
Neutropenia	CBC with differential before every dosing of antibody	Grade 3 (ANC 0·5–1·0 × 10⁹/L) without fever: continue treatment; consider the use of G-CSF until ANC>1·0 × 10⁹/L; grade 4 (ANC <0·5 × 10⁹/L) or febrile neutropenia: hold antibody and use G-CSF until ANC>1·0 × 10⁹/L; consider extending the dosing interval if desired response is achieved and myeloma under better control; consider prophylactic use of G-CSF when restarting antibody*
Anaemia	CBC with differential before every dosing of antibody	Grade 3 (haemoglobin <8 g/dL) or if patient is symptomatic: consider transfusing to keep haemoglobin >8 g/dL or treatment with erythropoietin-stimulating agents per institutional guidelines†
Thrombocytopenia	CBC with differential before every dosing of antibody	Grade 4 (platelets <25 000) without bleeding or grade 3 (platelets 25 000–50 000) with bleeding: hold antibody dosing until platelets recover to >50 000

ANC=absolute neutrophil count. CBC=complete blood count. *Recommend antibiotic, antiviral, antifungal prophylaxis, recommend monthly IVIG, recommend neutropenia work up including checking for cytomegalovirus, Epstein-Barr virus, and adenovirus. †Recommend checking for other causes of anaemia (vitamins, parvovirus, myelodysplasia).

Table 3: **Management of haematological adverse events related to bispecific antibodies**

Infections: monitoring, prophylaxis, and treatment

Incidence and severity across the different programmes

Infections are common complications seen in patients treated with bispecific T-cell engagers, particularly with BCMA-targeted agents. Ongoing T-cell activation, T-cell exhaustion, or treatment-induced depletion of some T-cell populations in addition to hypogammaglobinaemia and neutropenia might partially explain the high risk of infections seen in patients treated with bispecific antibodies. However, there is still a scarcity of detailed information about infectious risk and the pathogens involved.

The overall incidence of any-grade infection ranges from 32% with ABBV-383 to 76·4% with teclistamab, with severe grade 3–4 infections seen in 9–45% of cases across the different trials[5,6,9–11,25,27,28] (appendix pp 7–8). Differences in incidence could account for differences in the target, drug design, schedule, and duration of therapy as well as differences in median follow-up in the different trials, with clinical trials that have a longer follow-up having the highest cumulative incidence of infections. Clinical trials of BCMA bispecific antibodies have shown the highest incidence of infection, with more severe grade 3–4 infections[5,25,28,44] than clinical trials of non-BCMA bispecific antibodies. In the MonumenTAL-1 study, any-grade infections were reported in 84 (58·7%) of 143 patients in the 0·4 mg/kg once weekly dosing cohort and 96 (66·2%) of 145 patients in the 0·8 mg/kg once every 2 weeks dosing cohort, with grade 3–4 infections reported in 28 (19·4%) of 143 and 21 (14·5%) of 145 patients, respectively. New onset of grade 3–4 infections generally occurred in the first 100 days of therapy, whereas for BCMA bispecific antibodies the incidence is more or less constant throughout therapy.[45] Recent data on BCMA bispecific antibodies reported a decrease in the incidence of severe infections when switching from a once weekly to a once every 2 weeks dosing schedule, suggesting that less intensive dosing over time or fixed-duration dosing might mitigate the infectious risk.[46,47]

Overall, bacterial, fungal, and viral infections have all been reported in the different trials. Opportunistic

infections have also been reported, including cytomegalovirus (CMV; 11 [8·1%] of 123 patients treated with elranatamab), *Pneumocystis jirovecii* (six patients each in the MajesTEC-1 and MagnetiSMM-3 trials), adenovirus, parvovirus B16, herpes virus 6 (HHV6), or progressive multifocal leukoencephalopathy, among others.[5,6,10,11,28,39,44] CMV viraemia has been reported in some trials, although the overall frequency remains low (around 5%)[5,39] and the importance of this viral replication or reactivation is unknown. Notably, the incidence of CMV organ disease in the context of CMV viraemia appears low and thereby the value of pre-emptive therapy in the setting of bispecific antibody therapy is unclear and not recommended. Clinical judgement should be used when considering treatment for patients with CMV viraemia in the absence of CMV-related organ disease. In patients with clinical symptoms suggestive of CMV infection, antiviral treatment (with ganciclovir or valganciclovir) should be initiated, and bispecific antibody therapy should be placed on hold with active monitoring of the viral load.

SARS-CoV-2 infections and COVID-19-related deaths have also been frequently reported in the different clinical trials (appendix pp 7–8) that have been conducted during the COVID-19 pandemic. The overall incidence of COVID-19 ranges between 9% and 25%, with severe infections (grade 3–4) in 4–12% of patients treated. Incidence is higher with BCMA-targeting treatments as well as with cevostamab;[5,6,10,11,28,39,44] therefore, prevention and management of COVID-19 is essential. These drugs might also abrogate the production of COVID-19 antibodies in response to vaccinations.[48] Therefore, patients should be optimally vaccinated for COVID-19 and receive the appropriate booster doses, ideally before the initiation of bispecific antibody therapy. Hygienic measures for prevention of COVID-19 in bispecific antibody-treated patients, as well as testing for exposures and symptoms and initiation of appropriate oral or parenteral COVID-19 therapies (eg, nirmatrelvir with ritonavir, molnupiravir, and remdesivir) in COVID-19-positive patients is essential (appendix pp 9–11).

Endemic infections present in different countries around the world, such as tuberculosis, atypical mycobacteria, malaria, leptospirosis, and other re-emergent pathogens should be considered, monitored, and managed appropriately in patients receiving bispecific antibody therapy. Consultation and close collaboration with infectious disease specialists with experience in managing infections in immuno-compromised patients is paramount. Collating comprehensive data on infections and other complications with bispecific antibodies could be valuable for future guidance, and the IMWG Immunotherapy Database has been commenced to address some of these issues. The results of the IMWG panel survey are included in the appendix (pp 12–19) along with specific recommendations from the panel included in table 4 and the appendix (pp 9–11).

Infection management should continue even after discontinuation of bispecific antibody therapy since the risk of infections is not immediately resolved after treatment discontinuation. Additional studies are needed to better understand the duration of immunosuppression seen with these agents and its optimal management.

On-target, off-tumour toxicities

GPRC5D-targeted therapy-related adverse events

Co-expression of GPRC5D outside of the bone marrow leads to potential on-target, off-tumour effects. Although GPRC5D is highly expressed in multiple myeloma cells,[49,50] it is also expressed in cells that are able to produce hard keratin structures, such as hair follicles, and salivary glands.[51] As such, skin-related adverse events were reported in 20 (67%) of 30 patients treated with talquetamab at 0·4 mg/kg once weekly and 31 (70%) of 44 patients treated at 0·8 mg/kg once every 2 weeks.[6,41] The skin-related adverse events typically occurred early on during treatment, and all patients with grade 3 skin rash were successfully re-challenged without recurrence

	Agent or agents	Timing	Additional comments and recommendations
Antiviral: herpes simplex virus or varicella zoster virus	Aciclovir or valacyclovir	Throughout treatment	Continue for 3 months off treatment or until CD4 >200/μL
Pneumocystis	Trimethoprim/sulfamethoxazole, atovaquone	Throughout treatment	Continue until CD4 cell count >200/μL
Antibacterial	Local guidelines or quinolone	Neutropenia	Bacterial infection highest in first few cycles during neutropenia or if prolonged steroids needed
Antifungal	Local guidelines or azole	Neutropenia	Fungal infection risk low, consider during prolonged neutropenia or steroid use
Other viral; cytomegalovirus, hepatitis B virus	Entecavir for those at risk of reactivation	Throughout treatment	Cytomegalovirus PCR at start and if positive consider monitoring; local guidelines for monitoring versus preemptive treatment
Polymicrobial	Intravenous immunoglobulin	For IgG concentration <400 mg/dL	Hypogammaglobulinaemia is common throughout treatment; continue even off therapy for IgG concentrations <400 mg/dL

Table 4: **Infection prevention with bispecific antibody therapy**

of high-grade rashes. Nail-related adverse events were observed in 17 (57%) of 30 patients treated once weekly and 12 (27%) of 44 patients treated once every 2 weeks. Oral adverse events were commonly reported, with dysgeusia being the second most common non-haematological adverse event (incidence 19 [63·3%] of 30 once weekly and 25 [56·8%] of 57 once every 2 weeks). Oral adverse events tended be more gradual in onset compared to skin-related adverse events but often required continued attention by the health-care professional.

The mainstay of adverse event management with talquetamab is supportive care; however, dose interruptions or reductions might be required in severe or persistent cases. In a recent report the switch to less frequent dosing led to improvement in the oral and cutaneous toxicity related to talquetamab.[52] To prevent the onset of high-grade cutaneous adverse events, early or prophylactic use of emollients (eg, urea 10% cream or ammonium lactate 12% cream) and sunscreen is encouraged. Moreover, application of low-potency topical corticosteroids (eg, hydrocortisone and triamcinolone), with escalation to medium-potency corticosteroids, is recommended. For more extensive (ie, grade ≥3) rashes or rashes refractory to topical therapies, short courses of oral steroids (eg, prednisone or prednisolone) can be used. However, long-term corticosteroids should be avoided where possible due to the risk of infection. Rashes occurring beyond cycle 2 or refractory to emollients or low-potency steroids should prompt dermatology consultation.

Oral symptoms should be managed supportively, with dose interruptions or reductions reserved for severe or recurrent cases. Xerostomia can be managed with increased hydration (saliva substitutes), or sugar-free chewing gum to stimulate saliva flow. Sodium lauryl sulphate-free toothpastes might be better tolerated.[53,54] Nutritional supplements are recommended to optimise oral intake and limit bodyweight loss. The treatment of oral comorbidities (eg, Candida or thrush or nutritional deficiencies leading to glossitis) is also encouraged. Regular dental review is recommended to minimise the risk of periodontal disease and caries.[55]

Hypogammaglobulinaemia

Patients with relapsed or refractory multiple myeloma are at risk of hypogammaglobulinemia due to their underlying disease, which is further worsened by anti-myeloma treatments. Although patients with relapsed or refractory multiple myeloma are at an increased risk of infections, the preventive role of immunoglobulin replacement treatment (IVIG) remains unclear, with low quality evidence supporting its role.[56] However, there is emerging data that IVIG can protect against serious (grade ≥3) infections.[57,58] The expected incidence of serum IgG concentrations of up to 400 mg/dL during anti-BCMA therapy is higher than 50%, thus consensus recommendation, based on the infection-related fatalities observed,[5] is that all patients with IgG less than 400 mg/dL receive replacement IVIG.[57,58] In clinical trials, IVIG use was lower with talquetamab (range 9·7–13·3%) than with BCMA-targeting bispecific antibodies. However, IVIG should be considered in all patients with severe immunoparesis irrespective of the target, particularly if there is a risk of recurrent or severe infections.[57,58] However, it is important to highlight that the IgG concentration could be higher than the cutoff of 400 mg/dL due to the long half-life of IgG as well as a high prevalence of IgG-type myeloma, among other factors; therefore, it is important to evaluate IgA and IgM concentrations and subtract the amount of clonal IgG, and to consider an early start of IVIG replacement regardless of a particular cutoff, considering that the first infection event typically occurs early after the start of bispecific antibodies therapy.

Immune-effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome

Haemophagocytic lymphohistiocytosis-like manifestations, although infrequent, are being increasingly reported in the context of CAR-T cell therapies, broadly across patient populations and different constructs.[59] In an effort to improving patient outcomes in a difficult to diagnose but life-threatening complication, the American Society for Transplantation and Cellular Therapy Committee has published a consensus recommendation about the diagnosis and management of this entity now defined as immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome (IEC-HS).[59,60] Because CAR T-cell therapy and bispecific antibodies shared a common mechanism, IEC-HS can occur after bispecific antibody therapy, and physicians should remain vigilant. However, in the context of relapsed or refractory multiple myeloma, cases of IEC-HS related to bispecific antibody therapy have not yet been published nor publicly reported. If IEC-HS is suspected, additional immunosuppressive treatment should be considered, including steroids, etoposide, or anakinra (an IL-1 receptor antagonist),[60] among others.

In summary, various bispecific antibody-targeting agents are showing encouraging clinical efficacy in heavily pretreated patients with relapsed or refractory multiple myeloma and are being evaluated in the early disease setting, including frontline disease. However, these treatments are associated with unique toxicities, requiring appropriate training and education among health-care providers to minimise and prevent treatment-related adverse events and optimise patient care. These initial consensus guidelines are intended to help practitioners care for patients receiving these novel therapeutics. As greater experience is gained and additional agents are approved, these guidelines will be updated as appropriate.

Search strategy and selection criteria

A literature review was done in PubMed and Web of Science, restricted to publications published in English between Jan 1, 2022, and Oct 26, 2023. The search terms used were "multiple myeloma", "myeloma", "bispecific antibodies", "teclistamab", "talquetamab", "REGN5458/Linvoseltamab", "alnuctamab/CC93269", "elranatamab", "talquetamab", "cevostamab", "forimtamig", "RG6234", and "ABBV-383". This search yielded 293 results, which were assessed for relevance. For clinical trials with multiple data cutoffs, the most recent public data were used. Additionally, relevant abstracts presented in the latest congress of the American Society of Oncology, American society of Hematology, and International Myeloma Society were reviewed. We excluded clinical cases, letters, and editorial comments. We selected articles with at least 50 patients enrolled, as well as two consensus papers.

Contributors

All authors contributed to the systematic review and data generation, interpretation and critical review of all the data. All authors contributed to the survey. All authors had full access and provided final review of this manuscript. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

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