Managing side effects: guidance for use of immunotherapies in multiple myeloma

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Chimeric antigen receptor T-cell therapy and bispecific T-cell recruiting antibodies have transformed the treatment landscape for relapsed/refractory multiple myeloma, with B-cell maturation antigen being the most common target and other targets in clinical development. However, these therapies are associated with unique and severe toxicities, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), delayed neurotoxicity, cytopenias, and infection. In addition, immune effector cell-associated hemophagocytic lymphohistiocytosis (HLH)–like syndrome (IEC-HS), which exhibits overlap between CRS and HLH, can be challenging to diagnose and treat. In this review, we provide an overview of toxicities associated with novel immunotherapies for treatment of multiple myeloma and describe management recommendations. The pathophysiology and risk factors behind these toxicities are not yet comprehensively understood. Based on consensus recommendations, treatment for CRS consists of tocilizumab and steroids, while treatment for ICANS includes steroids and anakinra in severe cases. Management of cytopenias and infection is similar to post–hematopoietic cell transplantation principles with antimicrobial prophylaxis, growth factor support, immunoglobulin replacement, and vaccinations. In contrast, effective treatments for delayed neurotoxicity and IEC-HS are lacking, although steroids and anakinra are commonly used. Management of all these toxicities should include a broad differential and multidisciplinary collaboration with infectious diseases, neurology, and/or critical care providers.

LEARNING OBJECTIVES

- Recognize immunologically mediated toxicities with novel immunotherapies for multiple myeloma (chimeric antigen receptor T-cell and bispecific antibodies)
- Identify standard and emerging treatment options for cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and immune effector cell-associated hemophagocytic lymphohistiocytosis–like syndrome
- Evaluate and treat cytopenias following novel immunotherapies
- Understand key principles in preventing infection in patients with multiple myeloma treated with novel immunotherapies

CLINICAL CASE 1

A 65-year-old woman with a history of IgG κ multiple myeloma (MM) with high-risk features, including t(4;14), was initially treated with daratumumab, bortezomib, lenalidomide, and dexamethasone, resulting in a very good partial response. She received autologous hematopoietic cell transplantation (HCT), followed by daratumumab and lenalidomide maintenance. She relapsed within 1 year of HCT. After 3 subsequent lines of therapy, she underwent chimeric antigen receptor (CAR) T-cell therapy with ciltacabtagene autoleucel (cilta-cel). She received bridging therapy with a carfilzomib-based regimen, with progressive disease as best response. At time of lymphodepletion therapy, her M-spike was 2 g/dL, bone marrow showed 30% involvement with plasma cells, and positron emission tomography–computed tomography (PET-CT) had a few areas of fluorodeoxyglucose (FDG) avid disease.

On day 7 following CAR T-cell infusion, she developed fever and hypotension that responded well to intravenous (IV) fluids. Her absolute neutrophil count (ANC) count was 0.8×10^9/L. Infectious workup was sent, and she was started on broad-spectrum antibiotics for neutropenic fever. She was also deemed to have grade 2 cytokine release syndrome (CRS) and received tocilizumab 8 mg/kg IV and dexamethasone 10 mg IV once. C-reactive protein was

12 mg/dL and ferritin was 6000 ng/mL, both of which were significantly increased from baseline. Her fevers resolved with tocilizumab and dexamethasone, infectious workup was negative, and antibiotics were stopped after 48 hours. On day 9 following CAR T-cell infusion, she was noted to have word-finding difficulty, and immune effector cell-associated encephalopathy score was 8/10. She was deemed to have grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS) and received dexamethasone 10 mg IV, with resolution of symptoms. She was discharged from the hospital on day 12.

Introduction

CAR T-cell and bispecific T-cell engaging antibodies have emerged as promising treatments for relapsed/refractory MM. The current treatments approved by the US Food and Drug Administration (FDA), including idecabtagene vicluecel (ide-cel), cilta-cel, teclistamab and elranatamab, target B-cell maturation antigen (BCMA), although other targets like Fc receptor homolog 5 (FcRH5) and G-protein-coupled receptor family C group 5 member D (GPRC5D) are being explored in clinical trials and may become available as standard of care in the near future. Although these immunotherapies can lead to high overall response rates and durable responses, their use is limited by potentially severe and life-threatening complications, such as CRS, ICANS, delayed neurotoxicity, cytopenias, and infection (Figure 1). Prevention, monitoring, and management of these complications are crucial to improving patient outcomes.

Cytokine release syndrome

CRS occurs due to T-cell activation, proliferation, and systemic inflammation. It is seen with both CAR T-cell therapy and bispecific antibodies in MM. Clinical manifestations include fever and hypotension, while severe cases result in shock and multiorgan failure.[1] CRS is usually accompanied by changes in laboratory parameters, including elevated C-reactive protein, ferritin, lactate dehydrogenase, and coagulation labs. It is graded according to American Society of Transplantation and Cellular Therapy (ASTCT) criteria.[1] Most patients undergoing CAR-T therapy and two-thirds of patients receiving bispecific antibodies experience CRS, although grade 3 or higher CRS is less common.[2-8]

Table 1 shows CRS after BCMA-targeted immunotherapies, although the incidence of CRS appears to be similar regardless of the target antigen. For example, CRS was seen in 88% of patients undergoing GPRC5D CAR T-cell therapy with MCARH109[9] and in 70% to 80% receiving the non-BCMA-bispecific antibodies talquetamab (CD3×GPRC5D) and cevostamab (CD3×FcRH5), respectively.[10,11] CRS typically happens in the first few days of initiating therapy, with median time to onset for ide-cel and cilta-cel being 1 and 7 days, respectively.[2,3] It is possible that this difference in onset of CRS relates to the properties of the CAR T construct, cell dose, and subsequent time to CAR T-cell expansion. The target dose of cilta-cel is 0.5 to 1×10^6 CAR T cells/kg, and that of ide-cel is 300 to 460×10^6 CAR T cells; for a patient who weighs 100 kg and receives the higher end of the dose of cilta-cel, the overall dose of ide-cel is still 3 to 4 times higher. For bispecific antibodies,

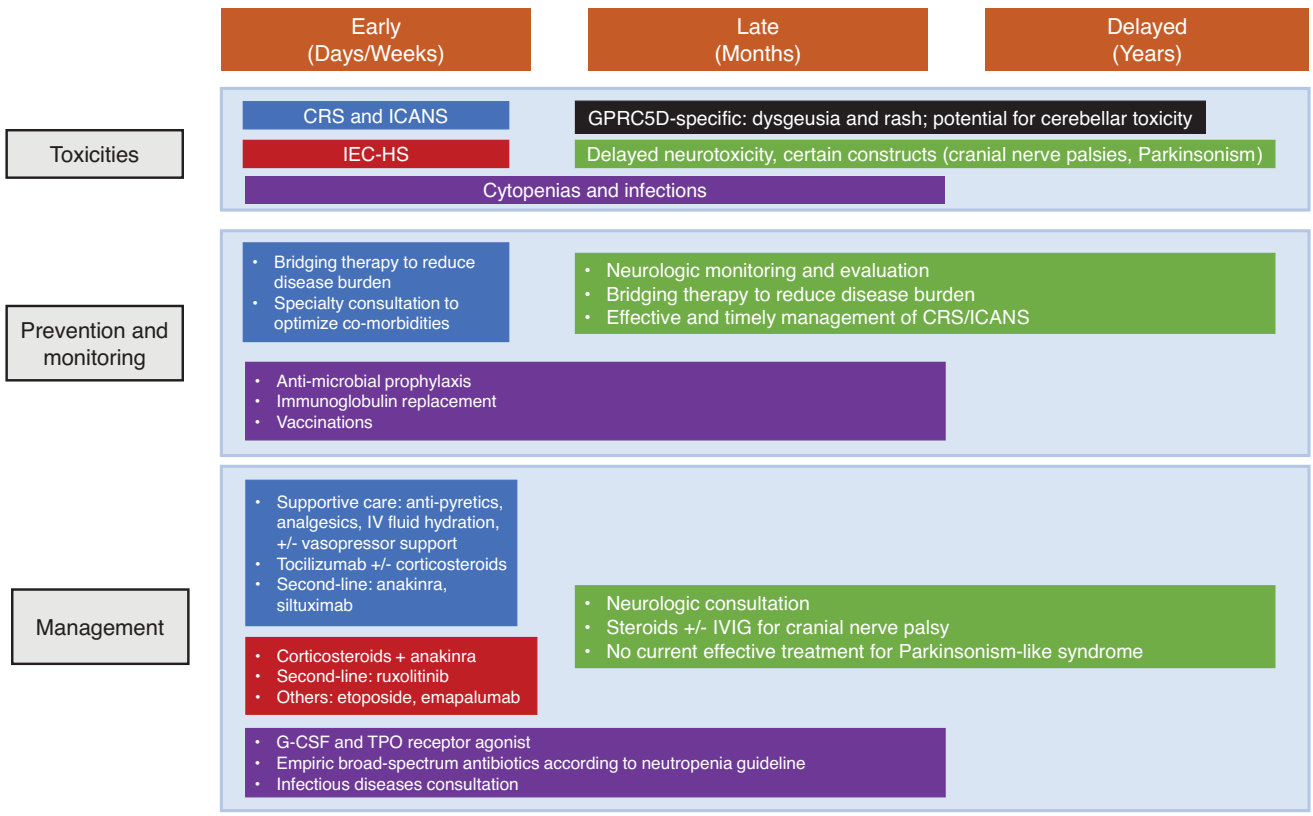

Figure 1. Early, late and delayed toxicities with CAR-T cell therapy and bispecific antibodies in multiple myeloma.

Table 1. CRS, ICANS, delayed neurotoxicity, and IEC-HS with BCMA CAR T-cell and bispecific T-cell recruiting antibodies

	Idecabtagene vicleucel (KarMMa)[1]	Ciltacabtagene autoleucel (CARTITUDE-1)[2]	Teclistamab (MajesTEC-1)[3]	Elranatamab (MagnetisMM-3)[4]*	Linvoseltamab (Linker-MM1)[5]*	Alnuctamab[6]*	ABBV-383[7]
CRS							
Any grade	84%	95%	72%	56%	44%	53%	57%
Grade ≥3	5%	4%	<1%	0%	1%	0%	2%
ICANS							
Any grade	18%†	17%	3%	3%	6%	3%	2%
Grade ≥3	3%	2%	0%	0%	1%	0%	N/A
Delayed neurotoxicity							
Any grade	—	12%	—	—	—	—	—
Grade ≥3	—	8%	—	—	—	—	—

1. Munshi et al,[2] *NEJM* 2021. 2. Berdeja et al,[3] *Lancet* 2021. 3. Moreau et al,[4] *NEJM* 2022. 4. Bahlis et al,[5] ASH 2022 presentation. 5. Bumma et al,[6] ASH 2022 presentation. 6. Wong et al,[7] ASH 2022 presentation. 7. D'Souza et al,[8] *JCO* 2022.

*Data from updated data presented at the 2022 American Society of Hematology Annual Meeting.

†Referred to as investigator-identified neurotoxicity.

CRS is usually limited to step-up doses and first full dose and occurs at median of 1 to 2 days after the dose.[4] Recurrence of CRS can be seen with subsequent bispecific antibody doses, although this is also typically limited to the first few doses.[5,12] Risk factors for development of CRS after CAR T-cell therapy, particularly severe CRS, are not well defined for myeloma, although disease burden is associated with higher-grade CRS after ide-cel,[13] similar to that seen for other hematologic malignancies treated with CD19-directed CAR-T cell therapy. The risk factors for CRS following bispecific antibody therapy are unknown.

Management of CRS is dependent on severity, and similar principles apply to CRS management with both CAR-T cell therapy and bispecific antibodies, with the notable addition for bispecific antibodies being to hold further doses until CRS has resolved. The FDA label for the only bispecific antibody approved to date, teclistamab, recommends step-up dosing with inpatient monitoring for CRS for 48 hours after administration of both step-up doses and first full dose and the lable for elranatamab recommends inpatient monitoring for 48 hours after first step-up dose and 24 hours after the second step-up dose. Both labels do not have specific guidelines on the use of tocilizumab and steroids for management, but these should be used similarly to CAR T-cell therapy. Patients with grade 1 CRS can be managed with close observation and supportive care, although many institutions use tocilizumab, an interleukin (IL) 6 receptor antagonist for grade 1 CRS, especially if persistent. Grade 2 CRS is managed with tocilizumab and steroids. Tocilizumab can be repeated every 8 hours usually for a maximum of 3 doses. For grade 2 CRS, steroid treatment is usually of limited duration and can be stopped once CRS resolves to grade 1. Grade 3 or 4 CRS is life-threatening and requires vasopressor support, along with tocilizumab, and high-dose corticosteroids in an intensive care unit, with potential use of other treatments if symptoms are not rapidly improving (Table 2).

While the role of tocilizumab and corticosteroids for CRS is well established,[2-4,7,8,14-18] the optimal treatment for CRS that is refractory to tocilizumab and corticosteroids remains unclear, and experiences are limited to retrospective or nonrandomized studies. Anakinra, an IL-1 receptor antagonist, is often used as second-line therapy for CRS.[19-22] For example, in 18 patients who developed CRS in the phase 1b/2 CARTITUDE-1 trial of cilta-cel, administration of anakinra at 100 to 200 mg every 8 to 12 hours over a median of 2.5 days led to CRS resolution in all but 1 patient.[21] Additional therapies for refractory CRS include siltuximab (anti–IL-6 monoclonal antibody),[23] etanercept (tumor necrosis factor α [TNF-α] inhibitor),[24] infliximab (anti–TNF-α monoclonal antibody),[16,25] and lenzilumab (anti–granulocyte-macrophage colony-stimulating factor monoclonal antibody).[26]

Similarly, prevention of CRS is an unmet need. All patients should have comorbidities optimized prior to CAR T-cell therapy. As disease burden is the strongest predictor for CRS,[14,27] prelymphodepletion bridging chemotherapy for patients with high tumor burden can be used as a mitigation strategy.[3] Other methods, such as prophylactic tocilizumab and anakinra, are currently being studied in patients with MM receiving bispecific antibodies[28] and in patients with B-cell non-Hodgkin lymphoma receiving CD19 CAR T-cell therapy[29-31] and, if effective, may be considered in the future.

CLINICAL CASE 1 (continued)

On day 16 of CAR T-cell therapy, the patient presented to the emergency department with right-sided facial droop consistent with a cranial nerve VII palsy. Workup for stroke, including magnetic resonance imaging (MRI) of the brain, was normal. Differential diagnosis included delayed neurotoxicity from cilta-cel vs cranial nerve VII palsy related to herpes zoster reactivation. There were no cutaneous lesions suggestive of herpes zoster, and she had also been on acyclovir prophylaxis. She was started on steroids with dexamethasone 4 mg twice daily and received intravenous immune globulin (IVIG). Her facial droop gradually improved over several days, although she developed side effects to steroids, which were decreased and then stopped after 2 weeks. Her facial droop continued to improve

Table 2. Prevention, monitoring, and management of CRS, ICANS, and delayed neurotoxicity

	Prevention	Monitoring	Management
CRS	Potential risk factors: high disease burden, aggressive disease • When clinically feasible, consider bridging therapy to reduce disease burden or use CAR-T cell therapy therapy in lower disease burden state	• Temperature and vital signs • Laboratory tests: CBC, chemistry, CRP, ferritin, coagulation studies	Any grade: • Supportive care: antipyretics • IV fluid hydration • Supplemental oxygen • Assessment of infection and, if neutropenic, empiric antibiotics per neutropenic guidelines Grades 1 and 2: consider tocilizumab for grade 1 CRS based on clinical features, especially if persistent. Recommend tocilizumab + corticosteroids for grade ≥2 CRS, with dosing and frequency based on severity. Grade ≥3: • Vasopressor support • Tocilizumab + corticosteroids • Second line: anakinra, siltuximab, etanercept, infliximab, lenzilumab
ICANS	Potential risk factors: disease burden, baseline elevated inflammatory markers, higher CAR T-cell dose • When clinically feasible, consider bridging therapy to reduce disease burden or use CAR T-cell therapy in lower disease burden state • Antiseizure prophylaxis	• Neurologic consultation in patients with preexisting neurologic disease • Baseline neurologic and mental status exams • ICE score every 8 hours • Neurologic checks at least every 8 hours • Airway monitoring	Any grade: • Supportive care: aspiration precautions, seizure prophylaxis • Corticosteroids: dosing and frequency dependent on severity • Consider CT head, MRI brain, EEG, and neurologic consultation Grade ≥3: • High-dose corticosteroids • Second line: anakinra, siltuximab
Delayed neurotoxicity	Risk factors: high disease burden, CRS, ICANS • Timely treatment of CRS/ICANS • When clinically feasible, consider bridging therapy to reduce disease burden or use CAR T-cell therapy in lower disease burden state	• Neurologic consultation in patients with preexisting neurologic disease • Neurologic evaluation up to 1 year after infusion to evaluate for cranial nerve palsies, neuropathy, and Parkinsonism	• Supportive care • Neurologic consultation • Cranial nerve palsies: corticosteroids, consider IVIG • No known effective therapy for Parkinsonian features
IEC-HS	Unknown	• As in CRS with close monitoring of blood counts, liver and renal function, and coagulation parameters	• Supportive care: antipyretics, analgesics, IV fluid hydration, vasopressor support, correction of coagulopathy • Corticosteroids + anakinra • Second line: ruxolitinib, etoposide, emapalumab, activation of CAR T-cell "kill switches" • Evaluation and treatment of alternative etiologies, including infection and progressive disease

CBC, complete blood count; CRP, C-reactive protein; EEG, electroencephalogram; ICE, immune effector cell-associated encephalopathy.

but had not completely resolved at last follow-up (8 weeks from CAR T-cell infusion).

Neurotoxicity

Neurotoxicity is another class effect seen with both CAR T-cell therapy and bispecific antibodies, with around 20% of patients experiencing it after CAR T-cell therapy, while the incidence is lower with bispecific antibodies (Table 1).[2-8] As shown in Table 1, up to 5% of patients develop ICANS after BCMA-targeted bispecific antibodies, though it has been seen in around 10% of patients after GPRC5D-targeted bispecific antibodies.[2-8] In a phase 1 dose escalation trial of GPRC5D CAR T-cell therapy with MCARH109, 1 patient experienced grade 4 ICANS at the highest dose level (450×10^6 CAR T cells).[9]

Neurotoxicity after immunotherapies typically manifests as ICANS in the first few days after infusion or initial doses, although other unusual delayed neurotoxicities have also been seen. Symptoms of ICANS include tremor, dysgraphia, expressive aphasia, and apraxia, and can progress to seizures and coma.[1] Neuroimaging is generally normal, but MRI can demonstrate cerebral edema or hyperintensities in the limbic system and brainstem.[1,32-34] Median time to onset of ICANS is 2 days after ide-cel[2] and 8 days after cilta-cel[3]; for bispecific antibodies, ICANS is usually restricted to the step-up doses and first full dose, with median time to onset of 2 to 3 days.[4,5,35]

While occasional cases of delayed neurotoxicities have been described with several BCMA-targeted CAR T-cell therapies, an unusually high incidence has been seen after cilta-cel. These delayed neurotoxicities include cranial nerve palsies, most commonly seventh nerve palsy, neuropathy, and Parkinsonism-like syndrome, which is characterized by movement, cognitive, and personality changes (also called movement and neurocognitive treatment-emergent adverse events, or MNTs). In the CARTITUDE-1 trial, cranial nerve palsies and MNTs occurred in 1 (1%) and 5 (5%) patients, respectively[36]; in CARTITUDE-4, the incidences of cranial nerve palsies and MNTs were 9% and 0.5% (n=1), respectively.[37] In addition, a real-world study

of cilta-cel observed a 12% incidence of delayed neurotoxicities, most of which were cranial nerve palsies (MNTs, 1%).[38] The median time to onset of these delayed neurotoxicities was 3 to 4 weeks, although they have been reported to occur more than 3 to 6 months after CAR T-cell infusion and can last through 1 year after infusion.[36,37,39-41] The mechanism behind these delayed neurotoxicities is unclear, but expression of BCMA at a low level in the parts of the central nervous system and trafficking of CAR T cells mediating on-target, off-tumor effects may play a role. Risk factors include preexisting CRS and ICANS and, similarly to CRS and ICANS, high disease burden and high CAR T-cell expansion.[36] Of note, all 6 patients who developed MNTs on CARTITUDE-1 and CARTITUDE-4 were male.[36,37] In the phase 1 studies of the GPRC5D-targeted CAR T-cell products MCARH109 and CC-95266, cerebellar neurotoxicity, such as dizziness and ataxia, were observed at incidences of 12% (n=2) and 13% (n=9), respectively, with a potential mechanism being GPRC5D expression in the cerebellum.[9,42] Patients should be educated and closely monitored for symptoms of delayed neurotoxicity, including by neurological exam that includes evaluation for gait, tremor, and handwriting changes and by neuroimaging, with the caveat that neuroimaging is often normal.[36,40]

Currently, treatment of ICANS consists of supportive care, corticosteroids, and anti-inflammatory agents such as anakinra and siltuximab in severe cases (Table 2).[15,17,34,36] Antiseizure prophylaxis is often used. Many centers use antiseizure prophylaxis in all patients undergoing CAR T-cell therapy, with dose increase at the time of ICANS development; in the case of bispecific antibodies, it is usually reserved for patients who develop symptoms of neurotoxicity given the low incidence of ICANS.

The treatment for delayed neurotoxicities is even more limited. Steroids are commonly used for treatment of cranial nerve palsies, often in conjunction with IVIG, and, in some cases, treatment for varicella zoster virus infection even in the absence of any lesions, although systematic data on efficacy are lacking. These cranial neuropathies often resolve, although time to resolution can be several weeks. MNTs are the most challenging delayed neurologic toxicities to manage, without any effective treatment option. Typical treatment for Parkinson disease has not been found to be effective. In patients who developed MNTs on CARTITUDE-1, steroids, systemic and intrathecal chemotherapy, anakinra, siltuximab, and neurologic agents such as carbidopa/levodopa did not improve symptoms.[36] Preemptive strategies include reducing tumor burden by use of effective bridging therapy and prompt treatment of CRS and ICANS. Neurologic consultation should also be performed prior to treatment in patients with preexisting neurologic disease to establish baseline symptoms and function, and patients should be monitored for up to 1 year following CAR T-cell infusion.[34,36]

Hemophagocytic lymphohistiocytosis (HLH)–like syndrome/immune effector cell-associated HLH-like syndrome

Hemophagocytic lymphohistiocytosis (HLH)–like syndrome/immune effector cell-associated HLH-like syndrome (IEC-HS) has been recently described as an entity distinct from severe CRS and is characterized as an hyperinflammatory syndrome with macrophage activation and HLH, worsening or new cytopenias, hyperferritinemia, coagulopathy, hypofibrinogenemia, and/or transaminitis.[43] Clinical trial reports of IEC-HS are limited to 1 patient on CARTITUDE-1.[3] In a single-center study of 55 patients undergoing BCMA CAR T-cell therapy, 12 (22%) developed IEC-HS.[44] Potential risk factors for IEC-HS include prior infection, longer CRS duration, grade ≥2 CRS, and neurotoxicity.[44]

Given the complexity and life-threatening nature of IEC-HS, a recent ASTCT working group developed consensus guidelines for diagnosing, grading, and treating IEC-HS.[43] Key components of management include rapid clinical identification; initial treatment with anakinra and corticosteroids; escalation to dual therapy with the addition of ruxolitinib, etoposide, and/or emapalumab; and evaluation of other etiologies of hyperinflammation, such as infection and progressive disease (Table 2).[43]

CLINICAL CASE 2

A 62-year-old man with standard-risk MM received teclistamab as 10th line for progressive disease and achieved a very good partial response after 6 months of therapy. IgG levels were low at 200 to 250 mg/dL, and he received IVIG once a month. During cycle 7 of teclistamab, he presented with fever and cough for 3 days. Chest imaging showed patchy ground-glass opacities bilaterally. He was thought to have coronavirus disease 2019 (COVID-19) pneumonia and was treated with a course of remdesivir with clinical improvement.

One month later, he presented again with fever. Infectious workup, including blood cultures and respiratory viral panel, was negative. He was started on broad-spectrum antibiotics. Given persistent fevers, he underwent CT chest, abdomen, and pelvis, which revealed pulmonary nodules. He was started on posaconazole. Four days after starting posaconazole, liver function tests were noted to be increased. He continued to have fevers, so workup of viral reactivation was pursued, and he was found to have adenoviremia with a viral load of 105 000 copies/mL. He was started on cidofovir, which was complicated by acute kidney injury. Gradually, his viremia decreased and his fevers resolved.

Cytopenias

Similar to CD19-targeted immunotherapies, BCMA-targeted immunotherapies frequently result in cytopenias. In addition to the clinical trial experiences described in Table 3, retrospective studies of patients receiving BCMA CAR T-cell therapy have demonstrated prolonged acute and delayed cytopenias and B-cell aplasia lasting >30 days following CAR T-cell infusion.[45,46] Predictors of delayed count recovery included increased bone marrow disease burden and longer CAR T-cell persistence.[46] Longer CAR T-cell persistence was also associated with slower recovery of IgA but not IgG or IgM.[45] There was no significant association between duration of cytopenias and CRS, number of lines of prior therapy, prior autologous hematopoietic cell transplantation, or peak CAR T-cell expansion.[46] In contrast, fewer lines of therapy predicted B-cell recovery at 3 months in both univariate and multivariable analyses.[45]

Table 3. Cytopenias and infection after BCMA CAR T-cell and bispecific T-cell recruiting antibodies

	Idecabtagene vicleucel (KarMMa)[1]	Ciltacabtagene autoleucel (CARTITUDE-1)[2]	Teclistamab (MajesTEC-1)[3]	Elranatamab (MagnetisMM-3)[4]*	Linvoseltamab (Linker-MM1)[5]*	Alnuctamab[6]*	ABBV-383[7]
Neutropenia							
Any grade	91%	96%	71%	48%	25%	37%	37%
Grade ≥3	89%	95%	64%	48%	23%	32%	34%
Thrombocytopenia							
Any grade	63%	79%	40%	30%	19%	24%	23%
Grade ≥3	52%	60%	21%	22%	16%	9%	12%
Anemia							
Any grade	70%	81%	52%	48%	36%	38%	29%
Grade ≥3	60%	68%	37%	37%	31%	25%	16%
Hypogammaglobulinemia							
Any grade	41%[8]	94%[9]	75%	75%	N/A	N/A	14%
Received IVIG	61%	38%	39%	41%	N/A	N/A	N/A
Infection							
Any grade	69%	58%	76%	67%	54%	34%	41%
Grade ≥3	22%	20%	45%	35%	29%	9%	N/A

1. Munshi et al,[2] *NEJM* 2021. 2. Berdeja et al,[3] *Lancet* 2021. 3. Moreau et al,[4] *NEJM* 2022. 4. Bahlis et al,[5] ASH 2022 presentation. 5. Bumma et al,[6] ASH 2022 presentation. 6. Wong et al,[7] ASH 2022 presentation. 7. D'Souza et al,[8] *JCO* 2022. 8. ABECMA FDA package insert. 9. CARVYKTI FDA package insert.

*Data from updated data presented at the 2022 American Society of Hematology Annual Meeting.

Management of cytopenias following BCMA-targeted immunotherapies is supportive. For early cytopenias (<30 days after CAR T-cell infusion), infectious prophylaxis and management as described below are critical. Granulocyte-colony stimulating factor (G-CSF) should be used during periods of prolonged neutropenia (ANC <500×10^9/L).[47] Protocols vary at each center, with some centers recommending G-CSF for ANC <1000 and others restricting it to ANC <500×10^9/L. Some centers also restrict use of G-CSF in patients with active or high-risk CRS due to initial reports of longer or more severe CRS after G-CSF administration in patients receiving CD19 CAR T-cell therapies,[48,49] although other studies report no association of G-CSF use with CRS or ICANS in BCMA CAR T-cell therapies.[50,51] In real-world studies of BCMA CAR T-cell therapy, approximately 90% of patients required G-CSF within 1 month of CAR T-cell infusion, with requirements decreasing over time.[52,53]

Treatment of prolonged or late cytopenias (>30 days after CAR T-cell infusion) consists of growth factor support with G-CSF, thrombopoietin-receptor agonists, and, for prolonged and late multilineage cytopenias, stem cell boost.[47] At this time, bone marrow evaluation for the presence of persistent or recurrent disease, opportunistic viral infections, marrow fibrosis, or secondary malignancy should be considered, particularly if there is no or minimal response to G-CSF.[47]

Infections

Infections occurred in over half of patients receiving BCMA-targeted immunotherapies on the pivotal clinical trials (Table 3).[2-5] Viral and bacterial infections are most common, although infections with fungal organisms such as *Aspergillus* and *Rhizopus* have also been observed.[2,52-56]

While prolonged hypogammaglobulinemia is a complication of both CD19- and BCMA-targeted immunotherapies, BCMA-targeted immunotherapies cause additional humoral immunodeficiency by destroying all plasma cells.[57,58] While rates of hypogammaglobulinemia and IVIG use have not been reported consistently across clinical trials (Table 3), retrospective studies of BCMA CAR T-cell therapy have demonstrated high rates of hypogammaglobulinemia.[45,52,54] Patients with severe infections had lower serum IgG concentrations than those with mild or moderate infections,[45] and infections tended to occur during periods of hypogammaglobulinemia.[52] In addition, patients receiving BCMA CAR T-cell therapy experienced a decline in pathogen-specific antibody titers to vaccinations[54] and, in 1 cross-sectional study, were half as likely to have seroprotective antibody titers and had fewer IgG-targeted pathogen-specific epitopes compared to patients receiving CD19 CAR T-cell therapy.[59]

Thus, prevention of infections after BCMA-targeted immunotherapies is critical. Following CAR T-cell therapy, patients should receive polymicrobial prophylaxis, including with trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* pneumonia prophylaxis and, during periods of prolonged severe neutropenia (ANC <0.5×10^9/L), levofloxacin and fluconazole (Table 4).[47,60] While similar principles of antimicrobial prophylaxis apply after bispecific antibody therapy, the duration of prophylaxis would depend on an individual patient's treatment duration and resulting cytopenias.

Table 4. Prevention of infectious complications and management of cytopenias resulting from CAR T-cell and bispecific T-cell recruiting antibodies

Intervention category	Intervention description	Indications	Notes
1. Antimicrobial Prophylaxis			
All patients			
Antiviral	Acyclovir or valacyclovir: prevention of HSV and VZV reactivation	All patients • CAR T-cell therapy: 12–18 months after infusion, at least until CD4 count >200/μL • Bispecific antibodies: during treatment and until 1 month after treatment discontinuation	
Pneumocystis jirovecii	Trimethoprim-sulfamethoxazole	All patients • CAR T-cell therapy: 12–18 months after infusion, at least until CD4 count >200/μL • Bispecific antibodies: during treatment and until 1 month after treatment discontinuation	Alternatives: dapsone, atovaquone, pentamidine (disadvantages include lack of activity against encapsulated organisms)
Selected patients			
Antiviral	Entecavir	Prevention of HBV reactivation in patients with history of HBV infection or known exposure	
Antibacterial	Levofloxacin	Consider during periods of prolonged severe neutropenia (ANC <0.5×10^9/L)	
Antifungal	Fluconazole or posaconazole	During periods of severe prolonged neutropenia (ANC <0.5×10^9/L) or prolonged steroid therapy	
2. Growth factors	G-CSF Thrombopoietin-receptor agonist	• Consider G-CSF if ANC <1.0×10^9/L; strongly recommend for ANC <0.5×10^9/L, especially if prolonged • Give G-CSF for active neutropenic infection • Consider TPO agonist if prolonged severe thrombocytopenia that persists beyond 30 days with high transfusion needs	• Caution in patients with active or high risk of CRS
3. Immunoglobulin replacement	IVIG 400–500 mg/kg	Serum IgG ≤400 mg/dL	Monitor serum IgG levels every 4 weeks
4. Vaccinations	Influenza COVID-19	Influenza vaccine repeated annually COVID-19 vaccine series repeated ≥3 months after CAR T-cell therapy If feasible, patients should be vaccinated prior to therapy.	Consider measuring serum pathogen-specific IgG titers after vaccination to evaluate for seroprotection. There are limited data to comment on repeating routine immunizations following CAR-T therapy and bispecific antibodies.

HBV, hepatitis B virus; HSV, herpes simplex virus; VZV, varicella zoster virus.

There are limited data to recommend standard post-cellular therapy vaccinations, although COVID-19 revaccination and influenza vaccination are highly recommended. If feasible, patients should be up to date on all appropriate vaccines prior to the start of therapy. Pathogen-specific IgG titers should be considered and more data are needed to recommend universal revaccination after CAR T-cell therapy, similar to post-HCT management (Table 4).

There is no clear consensus for monitoring or treating hypogammaglobulinemia after CAR T-cell or bispecific therapy. Rates of immunoglobin replacement therapy in clinical trial and real-world studies range from 13% to 62%.[2,52,53] According to consensus and expert recommendations, IgG replacement should be considered in patients with serum IgG ≤400 mg/dL, those with serious or recurrent bacterial infections, and those with low pathogen-specific antibody titers (Table 4).[17,60-62] Lastly, during periods of prolonged neutropenia or active neutropenic infection, G-CSF should be considered.[17,47]

It is important to note that viral reactivations with viruses like cytomegalovirus, human herpesvirus 6, Epstein-Barr virus, and adenovirus have been seen after both CAR T-cell therapy and bispecific antibodies.[10,55,56,63,64] Viral reactivation

should be strongly considered in the differential diagnosis when patients present with fever or other unexplained laboratory abnormalities. Viral levels should be evaluated in patients with fever without a clear explanation, especially in conjunction with findings such as liver function abnormalities and cytopenias.

The risk of infections with novel immunotherapies may be target dependent, as the risk of grade ≥3 infections, neutropenia, and hypogammaglobulinemia has been seen to be higher with BCMA-targeted bispecific antibodies compared with GPRC5D-targeted antibodies,[4,5,8,10,56] although additional follow-up and data are needed.

Unique toxicities of other MM targets

Other MM targets under investigation include FcRH5, which is expressed only on B cells, and GPRC5D, which is expressed on plasma cells and keratinized tissues. Similarly to the BCMA-targeted immunotherapies, common toxicities include CRS and cytopenias.[10,65,66]

Unique toxicities with GPRC5D-targeted immunotherapies relate to their effect on keratinized tissues. Such toxicities include skin-related events (dry skin, eczema, pruritus, hyperpigmentation), nail-related events (discoloration, dystrophy, hypertrophy, onycholysis), and dysgeusia, which occurred in up to 70% of patients on the phase 1 study of talquetamab.[10] These events tended to occur within 1 to 3 months of treatment and tended to resolve within 3 months, although nail changes can persist beyond 3 months; there were no treatment discontinuations related to these events.[10] Supportive care, including emollient creams and oral rinses, can be used for these symptoms.[66] Two patients (12%) experienced grade 1 dysgeusia after MCARH109, and it resolved in both patients without intervention.[9]

Conclusions

In conclusion, immunotherapies comprise a new treatment paradigm for patients with relapsed/refractory MM but are associated with unique, potentially prolonged immunologic, neurologic, hematologic, and infectious toxicities. As more of these promising therapies are developed, it is crucial for treating physicians to be able to recognize and treat these toxicities. Future work should focus on elucidating the pathophysiology and predictors of these toxicities and developing evidence-based management strategies to treat these toxicities.

Acknowledgments

Surbhi Sidana is supported by Stanford Cancer Institute/American Cancer Society Pilot Grant 2022 and Doris Duke Charitable Foundation.

Conflict-of-interest disclosure

Emily C. Liang: no competing financial interests to declare.

Surbhi Sidana reports consulting or advisory role for Janssen, Bristol-Myers Squibb, Magenta Therapeutics, Sanofi, and Takeda; research funding from Novartis, Janssen, Magenta Therapeutics, Allogene Therapeutics, and Bristol-Myers Squibb.

Off-label drug use

Emily C. Liang: There is no off label drug use.
Surbhi Sidana: There is no off label drug use.

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DOI 10.1182/hematology.2023000435