A Focus on CAR T-Cell Therapy and Bispecific Antibodies in Multiple Myeloma

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Authors' disclosures of conflicts of interest are found at the end of this article.

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https://doi.org/10.6004/jadpro.2022.13.5.13

Abstract

Significant strides have been made in the management of patients living with myeloma. However, patients with multiply relapsed or refractory multiple myeloma (MM) have a shorter overall survival; therefore, new treatments with novel mechanisms of action are needed in this patient population. Patients with relapsing disease require a full restaging work-up, including whole body imaging to evaluate for extramedullary disease and lytic bone lesions, as well as bone marrow biopsy with fluorescence in situ hybridization to determine if the patient has any new chromosomal changes that are present. Therapies utilizing the patient's immune cells, in particular T cells, provide a new option in relapsed/refractory myeloma. Treatment utilizing chimeric antigen receptor (CAR) T cells and/or bispecific antibody therapy provide excellent response rates. As such, advanced practitioners need to be aware of the potential toxicities associated with these newer treatments and how to manage them. This article will focus on the management of patients with relapsed and/or refractory disease who are undergoing treatment with either CAR T-cell therapy or bispecific T cell engager therapy.

CASE STUDIES

Case Study 1: CAR T-Cell Therapy

Mr. G is a 60-year-old Spanish-speaking Hispanic gentleman who lives in a rural town in the Southwest United States and was diagnosed with standard risk IgG lambda myeloma, International Staging System (ISS) stage II (beta-2 microglobulin 4 and albumin 3.1). He was diagnosed after presenting to his primary care provider with shortness of breath and was found to have a hemoglobin of 9.4 with normal iron studies. He was referred to an oncologist. His workup is shown in Table 1.

His local oncologist started him initially on bortezomib and dexamethasone. Once insurance approval was obtained for lenalidomide, it was added to his regimen at a dose of 25 mg orally days 1 to 21, ev-

J Adv Pract Oncol 2022;13(Suppl 4):31–43

Table 1. Initial and Restaging Workup for Mr. G

Laboratory data	Radiology	Pathology
Initial workup		
• SPEP IgG lambda M protein 3.2 • Lambda 300 • Kappa 3.2 • k/l ratio 0.01 • UPEP 254 mg/24 hours of Bence-Jones • Calcium normal • Creatinine 1.3	• FDG avid bone lesions	• 70% lambda light chain restricted plasma cells • 46 XY • FISH +t(11:14)
Restaging workup		
• SPEP IgG lambda M protein of 2.5 • Lambda light chain 125 • Kappa 2.3 • k/l ratio 0.01 • UPEP 100 mg/24 hours of Bence-Jones	• PET scan FDG avid bone lesions at T6, T12, and right humerus	• 60% plasma cells with lambda light chain restriction • FISH t(11:14) and t(4:14)

Note. SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; FDG = fluorodeoxyglucose; FISH = fluorescence in situ hybridization.

ery 28 days. He was subsequently referred to an academic center for consideration of stem cell transplant. He completed four cycles of bortezomib, lenalidomide, and dexamethasone, then underwent an autologous stem cell transplant with standard-of-care melphalan. At 90 days following stem cell transplant, Mr. G was placed on lenalidomide maintenance therapy. Unfortunately, he progressed after 4 months of therapy. Mr. G's therapy was switched to daratumumab, lenalidomide, and dexamethasone. He achieved a partial response (PR) and remained on this regimen for 6 months when he developed symptomatic disease progression in the form of new bone lesions. His therapy was then changed to carfilzomib, cyclophosphamide, and dexamethasone. He had a minimal response to this regimen and remained on therapy for 5 months. However, he developed progressive disease (Table 1). His past medical history is notable for hypertension and aspergillus, and the latter was treated with voriconazole. Due to progressive disease, standard-of-care options compared with a clinical trial with CAR T-cell therapy was discussed with him. Since he had a short duration of response to autologous stem cell transplant and a daratumumab-based regimen, chimeric antigen receptor (CAR) T-cell therapy was recommended.

Using a translator, discussion was held with Mr. G regarding CAR T-cell therapy. When discussing CAR T-cell therapy, it is important patients understand the complexities involved with this therapy. Patient education is important, and for patients whose primary language is not English, it is important to have patient education materials in their language. With the assistance of a Spanish translator, Mr. G was provided with information on potential toxicities, including myelosuppression, cytokine release syndrome (CRS), neurotoxicity, caregiver requirements, local housing requirement, and infection risk. Based on his recently progressive disease, bridging therapy intended to keep him in remission during the harvest and production process was also discussed (Gray, 2021).

Mr. G was concerned about the housing options for 30 days as he lives 7 hours from the academic center. In order to address his housing concern, he met with the center social worker. When patients undergo CAR T-cell therapy, they are required to have a caregiver with them for 30 days and to stay in the local area. Both of these requirements may be a hardship for patients, so it is important to disclose this up front and connect them with a social worker who can oftentimes be of assistance. During the visit, other options were discussed with him, as well as the risk and benefits of those therapies. After discussion, Mr. G decided to proceed on the clinical trial with CAR T-cell therapy. The social worker provided him with a list of housing

options in the area and subsequently was able to find housing at a housing center for patients with cancer in the area.

Case Study 2: Bispecific Antibodies

Mrs. S is a 66-year-old African American female presenting with multiple myeloma, IgG kappa ISS stage III (beta-2 microglobulin 6.3 and albumin 4.3) and symptoms of back pain and anemia. On initial workup, she was found to have t(4:14) (Table 2). She has a past medical history of type 2 diabetes mellitus and iron deficiency anemia. She is widowed and lives with her daughter and granddaughter.

She received bortezomib, lenalidomide, and dexamethasone for four cycles and then proceeded onto autologous stem cell transplant with standard-of-care melphalan. She was placed on lenalidomide 15 mg as maintenance therapy for 5 years until her first relapse, M-spike of 1.2 g/dL, IgG 2,000 mg/dL, and kappa free light chain of 500 mg/L. She was then placed on carfilzomib and dexamethasone for disease progression but developed a biochemical relapse after 6 months. As a result, lenalidomide was added. She achieved a partial remission for 6 months. At the time of relapse, a new bone marrow biopsy was performed, which showed 20% to 30% plasma cells with kappa light chain restriction. FISH revealed t(4:14) and gain of 1q21. She was placed on daratumumab, pomalidomide, and dexamethasone, and achieved a partial remission and remained on therapy for 12 months. She presented with new left rib pain, grade 1 anemia, and a rising M protein. Her diagnostic workup revealed new fluorodeoxyglucose (FDG) avid bone lesions and a heavily infiltrated marrow (Table 2).

The advanced practitioner (AP) presented Mrs. S with two clinical trial options and two standard-of-care options to treat her MM. The clinical trial options included CAR T-cell therapy and a BCMA-targeting bispecific antibody (BiAb). After discussing the risks, benefits, and alternatives with the AP and her oncologist, Mrs. S opted to enroll onto the BiAb clinical trial, as she continues to work part time in an office and was reluctant to spend an extended period of time in the hospital. She has a daughter who works full time and financially could not take time off of work to be a full-time caregiver if she opted for CAR T-cell therapy. She enrolled onto a clinical trial with teclistamab (JNJ-64007957) monotherapy.

Table 2. Initial and Restaging Workup for Mrs. S

Laboratory data	Radiology	Pathology
Initial workup		
• SPEP IgG kappa M protein 3.2 • Kappa FLC 550 mg/L • Lambda FLC 3.2 mg/L • k/l ratio 0.01 • UPEP 254 mg/24 hours of Bence-Jones • Calcium normal • Creatinine 0.9	• FDG avid bone lesions at T6 and T8	• 80% kappa light chain restricted plasma cells • 46 XX • FISH +t(4;14)
Restaging workup: 9/15/2020[a,b]		
• M-spike 3.5 • IgG 5,139 mg/dL • Kappa FLC 2,493 mg/L • Lambda FLC 8.1 mg/L • k/l ratio 307	• Interval increased FDG uptake in multiple hypermetabolic lesions as well as a new soft tissue lesion on the 7th left rib	• 90% kappa restricted plasma cells • FISH t(4:14); gain 1q21

Note. SPEP = serum protein electrophoresis; FLC = free light chain; UPEP = urine protein electrophoresis; FDG = fluorodeoxyglucose; FISH = fluorescence in situ hybridization.
[a]On 8/12/2020, M spike was 2.5, IgG 4,053 mg/dL, kappa FLC 1,163 mg/L, lambda FLC < 0.4 mg/L, and k/l ratio 2,909.
[b]On 7/14/2020, M spike was 2.3, IgG 3,995 mg/dL, kappa FLC 1,026 mg/L, lambda FLC < 0.4 mg/L.

While great strides have been made in the treatment of multiple myeloma, the disease remains largely incurable (Nandakumar et al., 2019). Patients remain at high risk for relapse; therefore, novel treatments that are more effective and tolerable are needed for patients with advanced relapsed and refractory multiple myeloma. In patients with penta-refractory disease, the overall survival is less than a year. It is in this group of patients that treatment options are greatly needed. In the past several years, chimeric antigen receptor (CAR) T-cell therapy and bispecific antibody (BiAb) treatment have been introduced in patients with refractory myeloma. This article will discuss therapeutic options of CAR T-cell therapy and BiAbs for refractory myeloma using a case-based approach.

OVERVIEW OF CAR T-CELL THERAPY

Over the past several years, various CAR T-cell products have been approved in the treatment of hematologic malignancies. More recently, the US Food and Drug Administration (FDA) approved idecabtagene vicleucel (ide-cel) for patients with relapsed/refractory myeloma who have had four or more prior therapies, including an immunomodulatory agent, proteasome inhibitor, and a CD38 monoclonal antibody.

CAR T-cell therapy begins with the collection and separation of T cells in the peripheral blood via apheresis (Adkins, 2019; Shank et al., 2017; Wudhikarn et al., 2020). Once the T cells are collected, a lentiviral or retroviral vector is used to deliver the gene to encode for the selected CAR into the patient's collected T cells. Once the gene is delivered, the T cells undergo transcription, and the T cells begin to express the targeted CAR. The T cells then undergo expansion until they reach the target cell dose. The cells are then shipped back to the infusion site in liquid nitrogen. Once the cells are received, the patient can begin the process of having the cells reinfused. Prior to infusion of the CAR T cells, patients undergo lymphodepleting chemotherapy usually with fludarabine and cyclophosphamide. The patient's cells are then reinfused 2 days later either in the inpatient or outpatient setting depending on the CAR T-cell product.

Once the cells are infused back into the patient, the CAR T cells undergo expansion. The CAR T cells will bind to a tumor antigen such as B-cell maturation antigen (BCMA) on the surface of the myeloma cells causing cell death (see Figure 1; Adkins, 2019; Shank et al., 2017; Wudhikarn et al., 2020). The main target in myeloma has been BCMA, as this particular antigen is expressed solely on malignant plasma cells and is important in myeloma cell growth and proliferation (D'Agostino, & Raje, 2019). However, other targets are being investigated, including SLAMF7, CD19, CD138, GPRC5D, and CD38 (Wudhikarn et al, 2020). Response rates with BCMA-directed CAR T-cell therapy in myeloma range from 57% to 98% (Table 3).

BRIDGING CHEMOTHERAPY

From the time the patient's T cells are collected, the time it takes for manufacturing can be up to 5 weeks. Patients with disease characteristics similar to those Mr. G has are often in active relapse when the decision to proceed to CAR T-cell therapy is made, and these patients will require bridging chemotherapy to control their disease until the T cells are harvested. Then, the CAR T cells are returned to the center and are ready for reinfusion.

To determine the ideal bridging regimen, clinicians must consider prior drug combinations, disease characteristics, and logistical challenges. The ideal bridging regimen should not result in significant infections, bleeding, or organ toxicity that could interfere with lymphodepleting chemotherapy and CAR T-cell infusion (Gray, 2021). However, salvage chemotherapy regimens with combinations of bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide (VTD-PACE) or similar can be used in certain situations when aggressive relapse requires disease control. To receive these therapies, patients are generally admitted to the hospital for at least a 5-day stay. A central venous access via infusion port or peripherally inserted central catheter (PICC) is required as doxorubicin is a vesicant.

Patients who receive VTD-PACE are at risk for short-term cytopenias once discharged from the hospital. Hematopoietic growth factors and prophylactic antibiotics with levofloxacin are

recommended if the absolute neutrophil count is less than 500 µL. Regular blood or platelet transfusions are often required for up to 3 or 4 weeks after VTD-PACE is given. If patients are in a community oncology setting, close communication with the referring center should be maintained (Brigle, 2021; Gray, 2021; Lee, 2003).

Case Study 1

Mr. G was admitted to the hospital for one cycle of VTD-PACE to control his disease. His blood count nadir was at day 10. Upon discharge from the hospital, he was started on levofloxacin 500 mg po daily until his absolute neutrophil count was over 500 µL. He was seen once weekly by the advanced practitioner (AP) and scheduled for possible red blood cell transfusions (if hemoglobin < 7.0 g/dL) or platelet transfusions (if platelet count < 10 µL). With the help of an interpreter, the AP reviewed signs of neutropenic fever and instructions if he developed a fever greater than 100.4°F. Fortunately, at day 22, his absolute neutrophil count recovered to over 1 µL and his platelets climbed to 122 µL. Myeloma labs showed a 50% decrease in his serum M-spike, and he was feeling well. Mr. G was scheduled for T-cell harvest. After his T cells were successfully collected, he was started on low doses of bortezomib, cyclophosphamide, thalidomide, and dexamethasone (intended to balance disease control and minimize risk of infection and complications) until his cells were manufactured.

Four weeks after T-cell harvest, Mr. G received leukodepletion chemotherapy in the outpatient setting with fludarabine and cyclophosphamide (FluCy) and was subsequently admitted to receive ide-cel. Upon admission for ide-cel, he was started on levetiracetam for seizure prophylaxis. On day 2 he developed fever, rigors, and wheezing. He required low flow oxygen support. His toxicity was graded as cytokine release syndrome (CRS) grade 2 due to the presence of fever and low-flow oxygen support. He remained normotensive.

TREATMENT OF CAR T-CELL RELATED TOXICITY

The main toxicities associated with CAR T-cell therapy include CRS, neurotoxicity, and myelosuppression (Adkins, 2019). As a result of CAR T cells binding to their antigen, the CAR T cells expand,

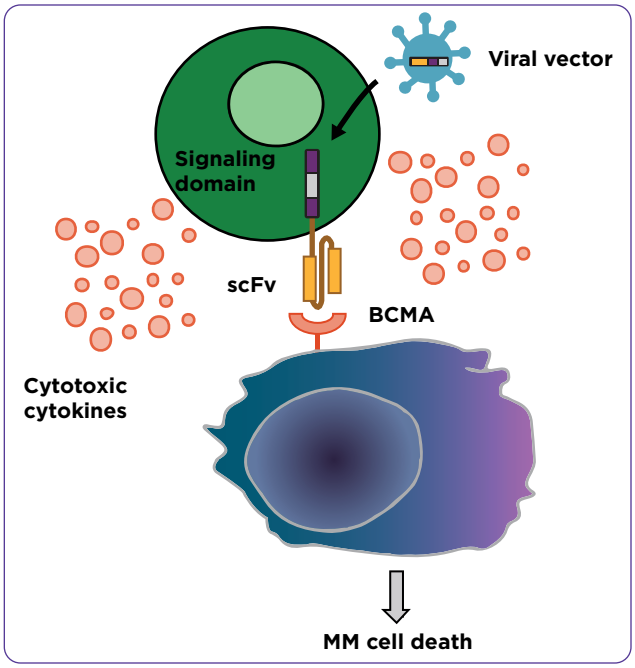

Figure 1. CAR T-cell therapy. Adapted from Yu et al. (2020).

releasing cytokines and subsequently causing destruction of tumor cells through the production of cytotoxic molecules. The release of cytokines such as interferon alpha, granulocyte macrophage colony-stimulating factor, interleukin 10, and interleukin 6 may result in third spacing as a result of increased permeability of the vasculature. This vascular permeability may result in vasodilation, volume depletion within the intravascular system, and cardiac output may decrease as well.

Cytokine Release Syndrome

The main symptoms observed with CRS include fever, hypotension, chills, and hypoxia. Other symptoms that may be observed with CRS include renal insufficiency, ventricular tachycardia, and atrial fibrillation. Grading of CRS is based on fever > 38°C, administration of vasopressors, and level of oxygen requirements (Table 4). The management of CRS is determined by the grade of the toxicity. For patients with grade 1, management usually consists of supportive therapy. In patients with grade 2 or higher, an anti-interleukin 6 receptor antagonist, tocilizumab, is administered and may also include steroids (Adkins, 2019). The onset of CRS differs between the different CAR T-cell products but generally ranges from 1 to 7 days.

Table 3. CAR T-Cell Therapy in Multiple Myeloma

CAR T-cell therapy	No. of prior lines of therapy	ORR	PFS (mo)	CRS all grades (grades 3/4)	ICANS all grades (grades 3/4)	Thrombocytopenia all grades (grades 3/4)	Neutropenia all grades (grade 3/4)	Onset to CRS
Ciltacabtagene autoleucel (CARTITUDE-1)	6	97.9%	66% at 18 mo	95% (4.1%)	21% (9%)	79.4% (59.8%)	96% (94.8%)	7 days
Ciltacabtagene autoleucel (CARTITUDE-2: 1–3 prior lines)	2	95%	90% at 6 mo	85% (10%)	15% (NR)	80% (35%)	95% (90%)	7 days
Idecabtagene vicleucel	6	73%	8.8 mo	84% (5%)	18% (3%)	63% (52%)	91% (89%)	1 day
Bb21217	6	69%	NR	75% (4%)	15% (4%)	NR	NR	2 days
CT053 (phase I)	4.5	87.5%	18.8 mo	62.5% (NR)	NR	NR (20.8%)	NR (85%)	1–4 days
CT053 (phase Ib/II; LUMMICAR-2)	6	100%	NR	86% (0%)	5% (0%)	NR (36%)	NR (100%)	2 days
P-BCMA-101	6	57% single agent; 73% with rituximab; 71% with lenalidomide	NR	25% (0%)	7% (2%)	NR (30%)	NR (74%)	NR

Note. ORR = overall response rate; PFS = progression-free survival; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome. Information from Anderson et al. (2021); Berdeja et al. (2021); Costello et al. (2020, 2021); Hao et al. (2020); Kumar et al. (2020); Martin et al. (2021); Munshi et al. (2021); Raje et al. (2021).

Table 4. ASBMT Grading of Cytokine Release Syndrome[a]

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[b]	≥ 38°C	≥ 38°C	≥ 38°C	≥ 38°C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or[c]:				
Hypoxia	None	Requiring low-flow nasal cannula[d] or blow-by	Requiring high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Note. Adapted from Lee et al. (2018). ASBMT = American Society for Blood and Marrow Transplantation; CRS = cytokine release syndrome; CPAP = continuous positive airway pressure; BiPAP = bilevel positive airway pressure.
[a]Organ toxicities associated with CRS may be graded according to Common Terminology Criteria for Adverse Events, version 5.0, but they do not influence CRS grading.
[b]Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who have CRS and then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In that case, CRS grading is driven by hypotension and/or hypoxia.
[c]Cytokine release syndrome grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as having grade 3 CRS.
[d]Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 liters/minute. Low-flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min.

The overall incidence of CRS in myeloma trials is 25% to 95%, with 2% to 10% as grade 3 or 4 (Anderson et al., 2021; Bahlis et al., 2021; Berdeja et al., 2021; Hao et al., 2020; Kumar et al., 2020; Martin et al., 2021; Raje et al., 2021).

Neurotoxicity

In addition to CRS, patients may develop neurotoxicity or immune effector cell-associated neurotoxicity syndrome (ICANS). Neurotoxicity in myeloma trials ranges from 7% to 21%, with 2% to 10% developing as a grade 3 or 4 (Anderson et al., 2021; Bahlis et al., 2021; Berdeja et al., 2021; Hao et al., 2020; Kumar et al., 2020; Martin et al., 2021; Raje et al., 2021). Symptoms may include dizziness, delirium, confusion, agitation, encephalopathy, or tremors (Adkins, 2019). While rare in myeloma, more severe neurotoxicity symptoms include seizures, cerebral edema, aphasia, obtundation, and leukoencephalopathy. Patients are placed on antiseizure prophylaxis with levetiracetam to prevent seizures and are monitored closely either in the hospital or as an outpatient using the immune effector cell-associated encephalopathy (ICE) tool (Table 5; Lee et al., 2019). Management of ICANS is dependent upon the severity and includes the use of steroids and if it occurs with CRS then the addition of tocilizumab is recommended (Table 6; Lee et al., 2019).

In addition to the risk for CRS and neurotoxicity, patients are at an increased risk of infection due to prolonged myelosuppression and hypogammaglobulinemia. Therefore, patients should be placed on antiviral, pneumocystis, and antifungal prophylaxis for 6 to 12 months after CAR T-cell therapy until the CD4 count is greater than at least 200 cells/mL (Santomasso et al., 2021). In patients with symptomatic hypogammaglobulinemia, consideration should be given to administer IV immunoglobulin monthly, particularly in those patients with an IgG level < 400

Table 5. Immune Effector Cell-Associated Encephalopathy Score (ICE)

Category	Points	Description
Orientation	4	Orientation to year, month, city, and hospital
Naming	3	Ability to name 3 objects
Following commands	1	Ability to follow simple commands
Writing	1	Ability to write a simple sentence
Attention	1	Ability to count backwards from 100 by 10

Table 6. Grading of Neurologic Events With the ASBMT ICANS Tool

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7–9	3–6	0–2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizures	NA	NA	Any clinical seizure, focal or generalized, that resolves rapidly; or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	NA	NA	NA	Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure/cerebral edema	NA	NA	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Note. Adapted from Lee et al. (2018). ASBMT = American Society for Blood and Marrow Transplantation; ICANS = immune effector cell–associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy; EEG = electroencephalogram; NA = not applicable. ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure/cerebral edema) not attributable to any other cause. For example, a patient with an ICE score of 3 who has a generalized seizure is classified as having grade 3 ICANS.

[a]A patient with an ICE score of 0 may be classified as having grade 3 ICANS if awake with global aphasia. But a patient with an ICE score of 0 may be classified as having grade 4 ICANS if unarousable.

[b]Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).

[c]Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE version 5.0 but they do not influence ICANS grading.

[d]Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to Common Terminology Criteria for Adverse Events, version 5.0.

mg/dL. Additionally, patients and their family members should receive the influenza and COVID-19 vaccines.

Case Study 1

Mr. G received acetaminophen and started on oxygen at 2 L via nasal cannula due to grade 2 CRS. He was also started on antibiotics with vancomycin and cefepime. Cultures were obtained, and a chest x-ray showed no consolidation. He received a dose of tocilizumab once. CT chest on day 2 revealed new opacities in the right lower lobe. Ferritin and C-reactive protein (CRP) rose to the highest level on day 2. His CRP went from 1.44 to 192.03 mg/L, and ferritin went from 162 to 400 ng/mL. On day 9, his handwriting changed, and he was unable to count backwards by 10 from 100. He was found to have grade 1 ICANS based on an ICE score of 8. Neurology was consulted, an electroencephalogram showed no seizure activity, and the MRI of the brain was unremarkable. He was monitored closely and had no further deterioration. He was discharged home on day 14 to be followed as an outpatient.

Mr. G stayed locally in Houston for 30 days (he was able to get assistance with housing through social work) and then was discharged to his local oncologist for monitoring (he lives 5 hours away). Mr. G received pentamidine every 3 weeks for *Pneumocystis jirovecii* pneumonia prophylaxis, valacyclovir for antiviral prophylaxis, and fluconazole for fungal prophylaxis for 6 months post therapy. Additionally, because his IgG level was low, it was recommended that he receive IV immunoglobulin monthly for the first 5 months until his IgG level was greater than 400 mg/dL.

He had an excellent response to CAR T-cell therapy, achieving a complete response with minimal residual disease negativity. A PET scan showed resolution of the FDG avid bone lesions. He remains off therapy almost 1 year post CAR T-cell therapy.

OVERVIEW OF BISPECIFIC ANTIBODIES

Bispecific antibodies are constructed to bind both to an antigen target on the surface of myeloma cells as well as to T cells, which leads to T/NK-cell activation resulting in destruction of the myeloma cells (Cho et al., 2018; Shah et al., 2020). The antibody contains an anti-CD3 antigen-binding site, which results in activation of the T cells to kill the specific tumor cell with the target antigen (Figure 2). Bispecific antibodies are characterized by their small size, which make them highly potent molecules, but also results in a shorter serum half-life (Cho et al., 2018). Due to the shorter half-life, the antibody does not stimulate persistent immunity; therefore, it is typically given on a frequent infusion schedule (weekly or biweekly) unlike CAR T-cell therapy (Klinger et al., 2012).

Bispecific antibodies differ from currently approved monoclonal antibodies, such as daratumumab or elotuzumab, because they bind to both the cytotoxic T cell and the malignant plasma cell. As the T cells are activated, a systemic inflammatory response called CRS may occur. Cytokine release syndrome is caused by the excessive and rapid release of cytokines into the blood when immune cells are activated. This results in fever and multiorgan dysfunction. Rates of CRS in BiAbs range between 24% to 77%, with the majority of events occurring at a grade 1 or 2 (Bahlis et al., 2021; Harrison et al., 2020; Moreau et al., 2021; Rodriguez et al., 2020; Zonder et al., 2021).

CLINICAL TRIAL DATA ON BiAbs

Bispecific antibodies are a novel treatment modality with encouraging results and acceptable safety profile in heavily treated patients. The main toxicities seen in clinical trials include CRS, myelosuppression, infections, and hypogammaglobulinemia. The main targets for BiAbs include BCMA, GPRC5D, CD38, and anti-FcRH5 (Lancman et al., 2021). In clinical trials of BCMA BiAbs, overall response rates (ORR) range between 26% to 83%, while rates for non-BCMA BiAbs are between 56% to 81% (Tables 7 and 8; Bahlis, et al., 2021; Costa, et al., 2019; Harrison, et al., 2020; Moreau et al., 2021; Rodriguez, et al., 2020; Topp et al., 2020; Zonder et al., 2021). The main adverse events observed with both BCMA and non-BCMA BiAbs include CRS, myelosuppression, infections, and fatigue. Although more data are needed, BiAbs will likely become an important part of the multiple myeloma treatment paradigm.

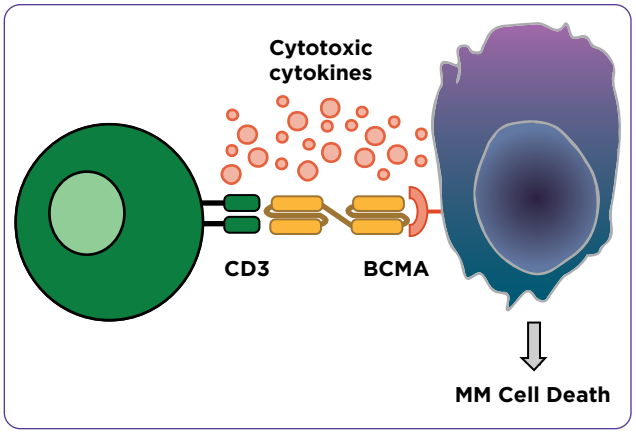

Figure 2. Bispecific antibodies. Adapted from Yu et al. (2020).

Case Study 2

Mrs. S received her first cycle with a step-up dosing approach to minimize CRS. Her first infusion took place in the outpatient infusion suite. She was then observed in the hospital with an additional step-up in dose. She experienced grade 1 CRS, presenting with a headache and a fever of 38.9°C 12 hours post dose. She was managed with supportive care measures of 1 g of acetaminophen every 4 to 6 hours as needed. Symptoms resolved within 24 hours. All subsequent doses were given without incidence.

During cycle 2, Mrs. S experienced a grade 2 neutropenia, which required no intervention. After 4 cycles of therapy, she was found to have resolution of PET avid bone lesions and her M-protein; thus, she achieved a complete response with minimal residual disease pending (Table 9). Her bone marrow showed less than 3% of CD138+ polyclonal plasma cells. She remains on therapy and is tolerating therapy well.

Table 7. BCMA-Targeted T Cell Engager Therapy

	AMG 701	CC-93269	Elranatamab	REGN5458	Teclistamab	TNB-383B
Treatment	Weekly IV	Weekly IV	Weekly SC	Weekly IV	Weekly SC	IV Q3W
Patients	N = 75	N = 19	N = 30	N = 68	N = 159	N = 103
Median prior lines	6	6	8	5	5	5
Triple-class refractory	68%	NR	87%	13.2%	77%	62%
ORR at therapeutic dose	36%	52.6%	75%	73.3%	65%	64%
Duration of response	3.8 mo	NR	NR	Not reached	90% at 6 mo	NR
Adverse events, all % (grade 3 and above, %)						
CRS	61% (7%)	90% (NR)	73% (0%)	38.2% (0%)	67% (1%)	52% (NR)
Infections	13% (NR)	NR (26%)	NR	NR	NR	28% (NR)
Neutropenia	23% (NR)	NR (53%)	40% (34%)	16.2% (13.2%)	53% (45%)	17% (NR)
Anemia	43% (NR)	NR (42%)	57% (46%)	NR	41% (27%)	9% (NR)
Thrombocytopenia	20% (NR)	NR (21%)	53% (40%)	NR	33% (18%)	14% (NR)
Other	Neurotoxicity 8% (0%)	–	ISR 53% (0%); ICANS 20% (0%)	ICANS (0%)	ICANS 2.5%	–
Deaths, n (%)	4 (5%)	1 (5%)	NR	NR	NR	5 (5%)

Note. IMiD = immunomodulatory drug; PI = proteosome inhibitor; dara = daratumumab; ISR = injection-site reaction; ICANS = immune effector cell-associated neurotoxicity syndrome; hypogamma = hypogammaglobulinemia. Information from Bahlis et al. (2021); Costa et al. (2019); Harrison et al. (2020); Kumar et al. (2021); Moreau et al. (2021); Rodriguez et al. (2020); Zonder et al. (2021).

Table 8. Non-BCMA Targeted T Cell Engager Therapy

	Anti-GPRC5D Talquetamab		Anti-GPRC5d Talquetamab + daratumumab	Anti-FcRH5 Cevostamab
Treatment	405 µg/kg SC QW (RP2D)	800 µg/kg SC QW	QW and 800 µg/kg Q2W	IV Q3W
Patients	N = 30	N = 23	N = 23	N = 160
Median prior lines	NR	NR	6	6
Prior BCMA therapy	30%	17%	NR	34%
Triple-class refractory	77%	65%	NR	85%
Penta-drug refractory	20%	22%	NR	68%
ORR at therapeutic dose	70%	71%	NR	160 mg 54.5%
Adverse events, all % (grade 3 and above, %)				
CRS	73% (3%)	78% (0%)	35% (0%)	80% (1%)
Infections	37% (3%)	13% (3%)	35% (17%)	43% (19%)
Neutropenia	67% (60%)	44% (35%)	39% (30%)	18% (16%)
Anemia	NR	NR	35% (22%)	32% (22%)
Thrombocytopenia	NR	NR	39% (22%)	NR
Other	–	–	Skin 65% Nail 17%	Neurologic 41% Diarrhea 26% (1%)
Deaths, n (%)	NR	NR	0	24 (15%)

Note. RP2D = recommended phase II dose; IMiD = immunomodulatory drug; PI = proteosome inhibitor; dara = daratumumab; ISR = injection-site reaction; ICANS = immune effector cell-associated neurotoxicity syndrome; hypogamma = hypogammaglobulinemia. Information from Chari et al. (2021); Krishnan et al. (2021); Trudel et al. (2021).

CONCLUSION

While many drug combinations are currently approved for use in patients with relapsed and/or refractory multiple myeloma who have progressed on multiple lines of therapy, the introduction of CAR T-cell therapy and bispecific antibodies offers hope for patients. Myeloma therapy is entering into an exciting time with the recent approval of a BCMA-directed CAR T-cell therapy, and others are in clinical development. In addition, bispecific antibody therapy will undoubtedly be a useful treatment, particularly in patients who may not be able to access CAR T-cell therapy due to their disease status or resources. Both therapeutic classes provide patients with new options and different targets, such as BCMA, CD138, SLAMF7, GPRC5D, and FCRH5. The future is bright for patients with relapsed/refractory myeloma.

Table 9. Disease response for Mrs. S

	M-spike	IgG mg/dL	Kappa FCL mg/L	Lambda FCL mg/L	Ratio	Radiology	Pathology
1/4/2021	0.0	600	19.2	13.9	1.38	Resolution of FDG avid lesions	CD 38+ polyclonal plasma cells involve less than 3% of marrow cellularity
11/1/2020 C2D1	0.8	1000	76.6	4.8	0.06		
9/15/2020 C1D1	3.5	5139	2493	8.1	307		
8/12/2020	2.5	4053	1163	< 0.4	2909		
7/14/2020	2.3	3995	1026	< 0.4			

Disclosure

Ms. Catamero has served on speakers bureaus for Oncopeptides and GSK and advisory boards for Bristol Myers Squibb, GSK, and Legend Biotech. Dr. Richards has served as a consultant for Bristol Myers Squibb, GSK, Janssen/Legend Biotech, Sanofi, and Takeda. Dr. Faiman has served as a consultant for Bristol-Myers Squibb, GSK, Janssen, Karyopharm, Legend Biotech, Oncopeptides, Sanofi, and Takeda.

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