Protracted viral infections in patients with multiple myeloma receiving bispecific T-cell engager therapy targeting B-cell maturation antigen

Recent expansion in therapeutic landscape in multiple myeloma (MM) has resulted in significant improvement in patient survival. Specifically, chimeric antigen receptor (CAR) T cells and bispecific T-cell engagers (BiTE) targeting B-cell maturation antigen (BCMA) have resulted in unprecedented response rates.[1] While infections remain the leading cause of morbidity and mortality in patients with relapsed/refractory multiple myeloma (RRMM),[2] the on-target-off-tumor toxicities associated with BCMA-targeting agents lead to prolonged B-cell aplasia, hypogammaglobulinemia, and increase the cumulative risk for infections.[3-6]

Currently, two CAR T cells and one BiTE product targeting BCMA are approved by the Food and Drug Administration (FDA) for the treatment of RRMM. Patients receiving these agents, either in clinical trials or commercially, need to have received several prior lines of treatment often including autologous hematopoietic cell transplant (autoHCT), monoclonal antibodies, and have prolonged cytopenia. This further intensifies the net state of immunosuppression, superimposed upon the immunoparesis associated with myeloma. Prior studies in BCMA CAR T highlighted an infection rate ranging between 23-63%.[3,4,7-9] A single-center study examined infections up to 1 year post CAR T in 55 patients and showed that 53% of infections were viral, 40% bacterial, and 6% fungal.[9] Another single-center study in 104 patients with RRMM and NHL undergoing BCMA and CD19-directed CAR T showed that BCMA CAR T-cell recipients had significantly more viral infections than CD19-directed CAR T recipients.[10] While there are evolving data among BCMA CAR T cell recipients, evidence remains limited among BCMA BiTE recipients.

In a single-center analysis of MM patients receiving BCMA CAR (n=26) and BiTE (n=36), CAR T recipients had higher baseline absolute lymphocyte counts (ALC) and were less heavily pretreated. The cumulative incidence and burden of infections was higher among BCMA BiTE compared to BCMA CAR T-cell recipients.[8] However, bacterial infections were predominant in this small study. A larger pooled analysis of ten clinical trials of MM BiTE in 790 MM patients (73% of patients treated with an agent targeting BCMA) showed grade 2-4 neutropenia in 37% and grade 3-4 infections in 26%. Importantly, non-BCMA targeted BiTE were associated with lower grade 2-4 neutropenia (45.6% *vs.* 24.4%) and lower grade 3-4 infections (27.5% *vs.* 16.9%) when compared to BCMA BiTE.[11]

Since CAR T-cell therapy is currently a one-time infusion, most patients may still achieve at least partial immune reconstitution with resolution of cytopenia and hypogammaglobulinemia.[4] Contrastingly, BiTE therapy is given indefinitely until disease progression or treatment intolerance. This can lead to a double-edged sword effect with BiTE therapy. While staying in remission, patients develop persistent plasma cell suppression, hypogammaglobulinemia, and suffer from significant morbidity due to recurrent infections, hospitalizations, and treatment interruptions. Herein, we present three cases of BCMA BiTE recipients who developed uncommon protracted viral infections (Table 1).

Case 1. A 73-year-old white male, with International Staging System (ISS) stage-3 IgA λ MM since March 2018 who had received six prior lines of treatment including autoHCT with melphalan 200 mg/m^2, remained in remission with a BCMA BiTE but developed parvovirus B19 infection. Patient's prior anti-myeloma treatment included immunomodulators (IMiD), lenalidomide and pomalidomide, proteasome inhibitors (PI) including carfilzomib, monoclonal antibody (mAb) targeting CD38 (daratumamab) and SLAMF7 (elotuzamab), BCL-2 inhibitor (venetoclax), and most recently a BCMA BiTE on a clinical trial initiated 3 years after the initial diagnosis of MM. The patient developed grade 1 cytokine release syndrome (CRS) with his first cycle of BCMA BiTE which resolved with tocilizumab.

Within 3 months of BiTE initiation, the patient developed symptomatic anemia with a drop in hemoglobin (Hb) to 5.9 g/dL. He did not exhibit occult signs of clinically bleeding and physical examination was unremarkable for jaundice, icterus, koilonychia, lymphadenopathy, or hepatosplenomegaly. Hematologic and gastrointestinal investigations were non-revealing except for hemolytic biochemical picture. Infectious disease (ID) work-up revealed parvovirus B19 infection (+ serum qualitative polymerase chain reaction [PCR]). The patient has been treated with monthly intravenous immunoglobulins (IVIG) and his Hb level remained above 10 g/dL consistently. His BCMA BiTE therapy was discontinued after 1.5 years due to recurrent infections which included chronic sinusitis and skin/soft tissue infections with resultant treatment intolerance. The patient continues to remain in clinical and biochemical remission of his myeloma to date, after being off treatment for 3 months. Immune correlates of disease and infection course are shown in Figure 1A.

Table 1. Patient, disease, and infection characteristics of bispecific T-cell engagers recipients.

Characteristic	Case 1	Case 2	Case 3
Age in years at MM diagnosis	69	50	58
Age in years at BiTE initiation	71	65	68
Age in years at infection diagnosis	71	65	69
Sex	Male	Male	Male
Race	White	White	White
Type of MM	IgA λ	IgA κ	IgA κ
Prior lines of therapy	4	7	10
Prior autoHCT	1	2	2
Number of cycles of BiTE	24	42	20
Duration of BiTE therapy in years	1.5	Ongoing	1
BiTE discontinued in months	Yes (off for 3)	NA	Yes (off for 17)
Current disease status	In remission	In remission	In remission
CRS at initiation of BiTE	Yes (grade 1)	No	Yes (grade 1)
Use of steroids/tocilizumab	Tocilizumab	NA	Tocilizumab
Viral infection	Parvovirus B19 (chronic)	Parvovirus B19	Norovirus
Diagnostic method	Parvovirus B19 DNA (qualitative PCR)	Parvovirus B19 DNA (qualitative PCR)	Stool norovirus (NAAT)
IgG level at the time of infection (mg/dL)	<40	<40	368
ALC level at the time of infection (x10^3 cells/uL)	3.59	0.33	0.25
Interval in months between infection onset and BiTE initiation	3	7	16
Treatment of infection	Monthly IVIG	Monthly IVIG	Monthly IVIG; nitazoxanide; stem cell boost
Outcome (resolution *vs.* ongoing *vs.* chronic *vs.* resistant)	Resolved	Resolved	Chronic

BiTE: bispecific T-cell engagers; MM: multiple myeloma; autoHCT: autologous hematopoietic cell transplant; CRS: cytokine release syndrome; DNA: deoxyribonucleic acid; PCR: polymerase chain reaction; NAAT: nucleic acid amplified test; IgA: immunoglobulin A; ALC: absolute lymphocyte counts; IVIG: intravenous immunoglobulins; NA: not analyzed.

Case 2. A 67-year-old white male was diagnosed with ISS stage 3A κ light chain MM in 2005 and received high-dose therapy (thalidomide/dexamethasone) followed by autoHCT. He then developed RRMM and received seven prior lines of treatment including two autoHCT with melphalan 200 mg/m^2 in 2005 and 2014. Prior MM treatment included IMiD: thalidomide, lenalidomide and pomalidomide, PI: bortezomib and carfilzomib, mAb elotuzamab and daratumamab. For the RRMM, he started BCMA BiTE in July 2020.

In February 2021, the patient presented with a cough and symptomatic anemia (Hb 9.8 g/dL) in the setting of profound hypogammaglobinemia (IgG <40 mg/dL). Physical examination was unremarkable for occult signs of clinical bleeding. Hematocrit was 23% with a reticulocyte percentage of 0.3%. A thorough ID workup revealed parvovirus B19 infection (serum qualitative PCR). The patient has been treated with monthly IVIG for persistent parvovirus B19. Despite persistent viremia, his Hb remains above 11 g/dL consistently and an IgG level of above 800 mg/dL. The patient has received 42 cycles of BiTE treatment over the last 2.5 years and maintains remission. The disease course is presented in Figure 1B.

Case 3. A 71-year-old White male was initially diagnosed with IgA κ MM with complex high-risk cytogenetics in 2008. He developed RRMM and received 10 lines of prior therapy including two autoHCT with melphalan 200

mg/m^2 in 2009 and 2012. Prior treatment regimens consisted of IMiD: lenalidomide, PI: bortezomib, oprozomib, and carfilzomib, and anti-CD38 mAb (daratumumab). For RRMM, he was enrolled in a clinical trial of BCMA BiTE in April 2020. The patient developed grade 1 CRS during initial infusion which resolved without further complications.

Seventeen months after BiTE initiation, he presented with severe diarrhea and abdominal pain. He had up to 25 loose non-bloody bowel movements daily. Physical exam was unremarkable for jaundice, hepatosplenomegaly, lymphadenopathy, or ascites. At the time of presentation, his IgG level was 368 mg/dL (Figure 1C). ID workup was negative for common enteric pathogen and colonoscopic biopsy pathological stains were negative for cytomegalovirus (CMV), herpes simplex virus (HSV), and adenovirus. Norovirus infection was diagnosed via stool PCR specimen, coupled with radiologic evidence of colitis. The patient was

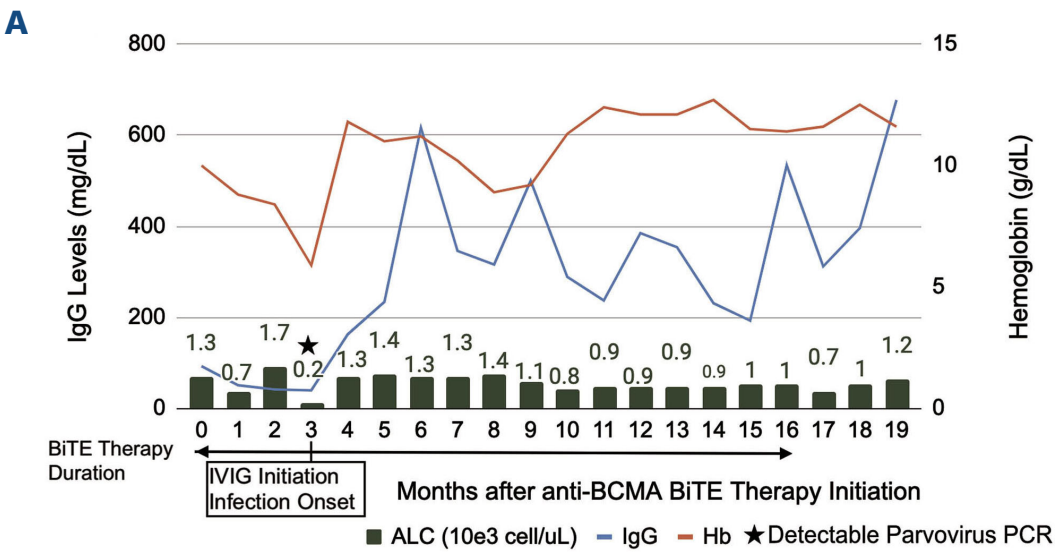

Figure 1. Immune correlates of the disease course, protracted viral infections, and treatment. (A) shows immune correlates of parvovirus B19 infection with absolute lymphocyte counts (ALC), immunoglobulin G (IgG), and hemoglobin (Hb) levels and the duration of bispecific T-cell engagers (BiTE) therapy; (B) shows the course of parvovirus B19 infection with ALC, IgG, and Hb levels with ongoing BiTE therapy; (C) illustrates the protracted course of norovirus infection, treatment with nitazoxanide and autologous stem cell boost, frequency of diarrhea, and the duration of BiTE therapy.

treated with 14-days of nitazoxanide, with transient improvement in symptoms. Diarrhea worsened significantly after nitazoxanide completion, and he persistently tested positive for norovirus. Monthly IVIG infusions were initiated for chronic hypogammaglobulinemia, but he continued to have diarrhea due to recalcitrant norovirus infection and discontinued BCMA BiTE infusion after 20 cycles (total duration, 1 year). In order to achieve immune reconstitution (including neutropenia), he received a stem cell boost using frozen stem cells collected during a prior remission. Upon last follow up, the patient remains in complete remission after discontinuing BCMA BiTE infusion for nearly 1.5 years. However, he continues to test positive for norovirus, although his diarrhea is slowly improving.

BCMA BiTE recipients develop distinctive infections with intracellular pathogens that may have a protracted course with frequent recurrences. BCMA targeting with bispecific T-cell engagement leads to persistent T-cell mediated cytotoxicity against plasma cells and B cells resulting in profound hypogammaglobulinemia.[6] Further, usage of immunosuppressive medications/premedications, CRS, impaired immune reconstitution, prolonged cytopenia, B-cell aplasia and potential redirection/activation of regulatory T cells contribute to a heightened infection risk in RRMM patients with pre-existing immune paresis.[1,6]

While it is difficult to discern the relative contribution of BiTE to the risk for infections as patients with RRMM are heavily pretreated with a profoundly and globally immunosuppressed state, severe and protracted infections could largely be attributed to anti-BCMA agents as these are associated with persistent B-cell and plasma cell suppression. Patients with RRMM receiving BiTE therapy are at a high risk for frequent viral infections/reactivations and transient viremia. These viral infections may include CMV, Epstein-Barr virus (EBV), parvovirus, HSV, BK polyomavirus viremia, and other visceral infections. Further, these patients are at a particularly high risk of chronic infections with SARS-CoV-2 and prolonged viral shedding.[12] Additionally, such patients may develop parvovirus-induced red cell aplasia as in our study. Additional infections that should be considered include adenoviral hepatitis, EBV-related lymphomas, progressive multifocal leukoencephalopathy due to John Cunningham virus, and Guillain-Barré syndrome.

As evident from the cases, use of prophylactic IVIG should be the standard of care. Comprehensive screening for viruses should be performed prior to initiation of BiTE and treatment postponed until complete eradication of any baseline active viral reactivation/infection. Active monitoring and surveillance for viruses such as CMV, EBV, SARS-CoV-2, and other community respiratory viruses should be pursued. A low threshold should be maintained for testing for appropriate pathogens based on apt clinical presentations (parvovirus, norovirus, HHV6B, etc). Pre-emptive antiviral therapy for CMV and EBV viremia with therapy interruption may be considered. Prophylactic antiviral therapy is essential. Since antibody synthesis is paralyzed in patients with RRMM, available strategies to provide passive immunity against ongoing viral infections such as against SARS-CoV-2 variants of concern should be considered and asymptomatic infections treated early to prevent progression. Evolving evidence further supports the use of additional (booster) vaccine doses.[13,14] Given significant risk of infections with prolonged use, examining BiTE therapies for RRMM on protocols with fixed duration or intermittent dosing are urgently needed. Meanwhile, comprehensive infection prevention strategies are urgently needed, particularly in patients with durable remission on ongoing therapy.[15]

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Contributions

BP and MBA drafted the manuscript. MBA, PH, and AD provided patient care and critically revised the manuscript. All authors were involved in the critical analysis and final version of the manuscript.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Lancman G, Sastow DL, Cho HJ, et al. Bispecific antibodies in multiple myeloma: present and future. Blood Cancer Disc. 2021;2(5):423-433.
2. Blimark C, Holmberg E, Mellqvist UH, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica. 2015;100(1):107-113.
3. Wang Y, Li C, Xia J, et al. Humoral immune reconstitution after anti-BCMA CAR T-cell therapy in relapsed/refractory multiple myeloma. Blood Adv. 2021;5(23):5290-5299.
4. Meir J, Abid MA, Abid MB. State of the CAR-T: risk of infections with chimeric antigen receptor T-cell therapy and determinants of SARS-CoV-2 vaccine responses. Transplant Cell Ther. 2021;27(12):973-987.
5. Hammons LR, Szabo A, Janardan A, et al. Kinetics of humoral immunodeficiency with bispecific antibody therapy in relapsed refractory multiple myeloma. JAMA Netw Open. 2022;5(10):e2238961.
6. Longhitano AP, Slavin MA, Harrison SJ, Teh BW. Bispecific antibody therapy, its use and risks for infection: Bridging the knowledge gap. Blood Rev. 2021;49:100810.
7. Mikkilineni L, Yates B, Steinberg SM, et al. Infectious complications of CAR T-cell therapy across novel antigen targets in the first 30 days. Blood Adv. 2021;5(23):5312-5322.
8. Mohan M, Nagavally S, Dhakal B, et al. Risk of infections with B-cell maturation antigen-directed immunotherapy in multiple myeloma. Blood Adv. 2022;6(8):2466-2470.
9. Kambhampati S, Sheng Y, Huang C-Y, et al. Infectious complications in patients with relapsed refractory multiple myeloma after BCMA CAR T-cell therapy. Blood Adv. 2022;6(7):2045-2054.
10. Kambhampati S, Fakhri B, Sheng Y, et al. Infectious complications of BCMA-targeted and CD19-targeted chimeric antigen receptor T-cell immunotherapy. Blood. 2020;136(Suppl):S4-5.
11. Mazahreh F, Mazahreh L, Schinke C, et al. Risk of infections associated with the use of bispecific antibodies in multiple myeloma: a pooled analysis. Blood. 2022;140(Suppl 1):S4378.
12. Abid MB, Mughal M, Abid MA. Coronavirus disease 2019 (COVID-19) and immune-engaging cancer treatment. JAMA Oncol. 2020;6(10):1529-1530.
13. Abid MA, Abid MB. SARS-CoV-2 vaccine response in CAR T-cell therapy recipients: a systematic review and preliminary observations. Hematol Oncol. 2022;40(2):287-291.
14. Abid MB, Rubin M, Ledeboer N, et al. Efficacy of a third SARS-CoV-2 mRNA vaccine dose among hematopoietic cell transplantation, CAR T cell, and BiTE recipients. Cancer Cell. 2022;40(4):340-342.
15. Haroon A, Muhsen IN, Abid MB, et al. Infectious complications and preventative strategies following chimeric antigen receptor T-cells (CAR-T cells) therapy for B-cell malignancies. Hematol Oncol Stem Cell Ther. 2022;15(3):153-158.