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Breanna Palmen\textsuperscript{1}, Parameswaran Hari\textsuperscript{2}, Anita D’Souza\textsuperscript{2}, Muhammad Bilal Abid\textsuperscript{1,2,3}

\textsuperscript{1}Medical College of Wisconsin, Milwaukee, WI, USA
\textsuperscript{2}Division of Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, WI, USA
\textsuperscript{3}Division of Infectious Diseases, Department of Medicine, Medical College of Wisconsin, WI, USA

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\textbf{Muhammad Bilal Abid, MD, MS, FACP, MRCP, FRCP}
Assistant Professor of Medicine
Divisions of Hematology/Oncology & Infectious Diseases
BMT & Cellular Therapy Program

Medical College of Wisconsin
Hub for Collaborative Medicine (Office - A8195)
8701 Watertown Plank Road, Milwaukee, WI 53226
P: 414.955.0521 I F: 414.955.0097 I mabid@mcw.edu
Pronouns: He/Him/His
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mabid@mcw.edu
REPORT:

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 (BiTEs) targeting B-cell maturation antigen (BCMA) have resulted in unprecedented response rates. While infections remain the leading cause of morbidity and mortality in patients with relapsed/refractory multiple myeloma (RRMM), 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.

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 with myeloma. Prior studies in BCMA CAR-T highlighted an infection rate ranging between 23%-63%. 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. Another single-center study in 104 patients with RRMM and NHL undergoing BCMA and CD19-directed CAR-T showed that BCMA CAR-T recipients had significantly more viral infections than CD19-directed CAR-T recipients. 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 CARs (n=26) and BiTEs (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 BiTEs compared to BCMA CAR-T
cell recipients. However, bacterial infections were predominant in this small study. A larger pooled analysis of 10 clinical trials of MM BiTEs in 790 MM patients (73% of patients treated with an agent targeting BCMA) showed grade II/IV neutropenia in 37% and grade III/IV infections in 26%. Importantly, non-BCMA targeted BiTEs were associated with lower grade II/IV neutropenia (45.6% vs. 24.4%) and lower grade III/IV infections (27.5% vs. 16.9%) when compared to BCMA BiTEs.

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. 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 3 cases of BCMA BiTE recipients who developed uncommon protracted viral infections (table 1).

**Case #1:**
A 73-year-old white male, with ISS stage-III IgA lambda MM since March 2018 who had received 6 prior lines of treatment including autoHCT with melphalan 200mg/m², remained in remission with a BCMA BiTE but developed parvovirus B19 infection. Patient's prior anti-myeloma treatment included immunomodulators (IMiDs), lenalidomide and pomalidomide, proteasome inhibitors (PIs) including carfilzomib, monoclonal antibody (mAb) targeting CD38 (daratumumab) and SLAMF7 (elotuzumab), BCL-2 inhibitor (venetoclax), and most recently a BCMA BiTE on a clinical trial initiated 3 years after the initial diagnosis of MM. 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, 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 nonrevealing except for hemolytic biochemical picture. Infectious disease (ID) work-up revealed parvovirus B19 infection (+ serum qualitative PCR). The patient has been treated with monthly intravenous immunoglobulins (IVIG) and his Hb level remained above 10g/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. 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.

Case #2:

A 67-year-old white male was diagnosed with ISS Stage IIIA kappa light chain MM in 2005 and received high-dose therapy (thalidomide/dexamethasone) followed by autoHCT. He then developed RRMM and received 7 prior lines of treatment including 2 autoHCT with melphalan 200mg/m2 in 2005 and 2014. Prior MM treatment included IMiDs: thalidomide, lenalidomide and pomalidomide, PIs: bortezomib and carfilzomib, mAb elotuzamab and daratumamab. For the RRMM, he started BCMA BiTE in July 2020.

In February 2021, patient presented with cough and symptomatic anemia (Hb 9.8 g/dL) in the setting of profound hypogammaglobinemia (IgG <40mg/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). Patient has been treated with monthly IVIG for persistent parvovirus B19. Despite persistent viremia, his Hb remains above 11g/dL.
consistently and an IgG level of above 800mg/dL. 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:
71-year-old Caucasian male was initially diagnosis with IgA kappa MM with complex high-risk cytogenetics in 2008. He developed RRMM and received 10 lines of prior therapy including 2 autoHCT with melphalan 200mg/m2 in 2009 and 2012. Prior treatment regimens consisted of IMiD: lenalidomide, PIs: bortezomib, oprozomib, and carfilzomib, and anti-CD38 mAb (daratumumab). For RRMM, he was enrolled in a clinical trial of BCMA BiTE in April 2020. 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 upto 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 368mg/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. Noroviral infection was diagnosed via stool PCR specimen, coupled with radiologic evidence of colitis. Patient was 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). 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. Further, usage of immunosuppressive medications/pre-medications, CRS, impaired immune reconstitution, prolonged cytopenia, B-cell aplasia and potential redirection/activation of regulatory T-cells further contribute to a heightened infection risk in RRMM patients with pre-existing immune paresis.

While it is difficult to discern the relative contribution of BiTEs 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. 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 (PML) due to John Cunningham (JC) 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 BiTEs 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). Preemptive 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\textsuperscript{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\textsuperscript{15}. 
REFERENCES:


Table 1: Patient, disease, and infection characteristics of BiTE recipients

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
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<tbody>
<tr>
<td>Age at MM diagnosis</td>
<td>69</td>
<td>50</td>
<td>58</td>
</tr>
<tr>
<td>Age at BiTE initiation</td>
<td>71</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>Age at infection diagnosis</td>
<td>71</td>
<td>65</td>
<td>69</td>
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<td>Gender</td>
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<td>Male</td>
<td>Male</td>
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<tr>
<td>Race</td>
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<td>White</td>
<td>White</td>
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<tr>
<td>Type of MM</td>
<td>IgA lambda</td>
<td>IgA kappa</td>
<td>IgA kappa</td>
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<td>Prior lines of therapy</td>
<td>4</td>
<td>7</td>
<td>10</td>
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<tr>
<td>Prior autoHCT</td>
<td>1</td>
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<td>2</td>
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<tr>
<td>Number of cycles of BiTE</td>
<td>24</td>
<td>42</td>
<td>20</td>
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<tr>
<td>Duration of BiTE therapy</td>
<td>1.5 years</td>
<td>Ongoing</td>
<td>1 year</td>
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<td>BiTE discontinued</td>
<td>Yes (off for 3 months)</td>
<td>N/A</td>
<td>Yes (off for 17 months)</td>
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<td>Current disease status</td>
<td>In remission</td>
<td>In remission</td>
<td>In remission</td>
</tr>
<tr>
<td>CRS at initiation of BiTE</td>
<td>Yes (Grade 1)</td>
<td>No</td>
<td>Yes (grade 1)</td>
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<td>Use of steroids/tocilizumab</td>
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<td>Viral infection</td>
<td>Parvovirus B19 (chronic)</td>
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<td>Norovirus</td>
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<tr>
<td>Diagnostic method</td>
<td>Parvovirus B19 DNA (qualitative PCR)</td>
<td>Parvovirus B19 DNA (qualitative PCR)</td>
<td>Stool norovirus NAAT</td>
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<td>IgG level at the time of infection (mg/dL)</td>
<td>&lt;40</td>
<td>&lt;40</td>
<td>368</td>
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<tr>
<td>ALC level at the time of infection (x 10^3 cells/uL)</td>
<td>3.59</td>
<td>0.33</td>
<td>0.25</td>
</tr>
<tr>
<td>Interval between infection onset and BiTE initiation</td>
<td>3 months</td>
<td>7 months</td>
<td>16 months</td>
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<tr>
<td>Treatment of infection</td>
<td>Monthly IVIG</td>
<td>Monthly IVIG</td>
<td>Monthly IVIG; nitazoxanide; stem cell boost</td>
</tr>
<tr>
<td>Outcome (resolution vs ongoing vs chronic vs resistant)</td>
<td>Resolved</td>
<td>Resolved</td>
<td>Chronic</td>
</tr>
</tbody>
</table>

**Abbreviations**: 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; IgG, immunoglobulin G; ALC, absolute lymphocyte counts; IVIG, intravenous immunoglobulins;
**Figure legend:** Immune correlates with the disease course of multiple myeloma and viral infections.

Figure 1A (top panel) shows immune correlates of parvovirus B19 infection with ALC, IgG, and Hb levels and the duration of BiTE therapy. Figure 1B (middle panel) shows the course of parvovirus B19 infection with ALC, IgG, and Hb levels with ongoing BiTE therapy. Figure 1C (bottom panel) illustrates the protracted course of norovirus infection, treatment with nitazoxanide and autologous stem cell boost, frequency of diarrhea, ALC, IgG, and the duration of BiTE therapy.