blood advances

Defining infection risk of bispecific antibodies for myeloma

Sarah P. Hammond

Divisions of Infectious Diseases and Hematology/Oncology, Massachusetts General Hospital; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Comment on Ludwig et al, page 4979

In this issue of *Blood Advances*, Ludwig et al[1] propose a standardized model for reporting infections in patients treated with bispecific antibody therapy for relapsed/refractory multiple myeloma. Considering the limitations of current clinical trial reporting practices that do not account for the duration of follow-up and typically report only the single highest grade infection per patient during the study (instead of reporting all infections per patient), the authors reviewed publications with ≥50 participants with myeloma treated with bispecific antibody monotherapy and determined infections per 100 patients per month to adjust for these limitations. Furthermore, they reviewed all infectious events per month adjusted by the number of participants in the MajesTEC trial[2] and found that the rates of all grades of infections per month were similar throughout the 18 months of follow-up. With this analysis, they have upended the idea that infectious risk is highest in the first few months after bispecific antibody therapy initiation. They have also shown that there is a steady infection rate over time, which implies that the infection risk is likely associated more with bispecific antibody therapy than with underlying uncontrolled myeloma at the outset of treatment.

Since the development and regulatory approval of bispecific antibodies for the treatment of relapsed/refractory multiple myeloma, it has become clear that infection is a major associated risk. Initial reports from clinical trials of bispecific antibodies targeting B-cell maturation antigen, Fc receptor-homolog 5, and G protein–coupled receptor, family C, group 5, member D (largely conducted during the early years of the COVID-19 pandemic) demonstrated high infection rates, though with some differences based on the bispecific antibody target. This subsequently triggered a call to improve the clarity and accuracy of infection reporting in ongoing trials[3] and led to a proliferation of guidance documents for the prevention of infection in patients with myeloma treated with these agents based on the limited data available.[4,5] Trials, meta-analyses, and small single-center studies have shown that bacterial and respiratory viral infections are common in this patient population.[2,6] Importantly, these studies have also highlighted that opportunistic infections more often seen with other intense cancer therapies (eg, allogeneic hematopoietic cell transplantation or alemtuzumab therapy) may also be associated with these therapies (see table) including disseminated adenovirus infection, cytomegalovirus (CMV) reactivation and progressive multifocal leukoencephalopathy due to JC virus.[6]

Postmarketing studies and single-center studies have also defined a few important risks for infection in patients with relapsed/refractory myeloma being treated with bispecific antibody therapy. Jourdes et al described the characteristics and incidence of infection in 229 patients treated with commercially approved agents including teclistamab, elranatamab, or talquetamab at 14 French centers and found that corticosteroid therapy for the management of cytokine release syndrome or immune effector cell associated neurotoxicity increased risk for first infection.[7] These authors also showed that it is common for patients to have >1 infection within several months of therapy. Lancman et al studied infection among 37 patients with multiple myeloma treated with bispecific antibodies at a single center between 2019 and 2022 and found that hypogammaglobulinemia was present in all responders to bispecific antibody therapy; they observed 90% fewer infections during times when patients were treated with IV immunoglobulin than when patients were off this therapy.[8] Similarly, Frerichs et al found that IV immunoglobulin replacement was associated with a significantly lower risk of serious infection in 52 patients treated with teclistamab.[9]

It is clear that both common as well as opportunistic infections are a risk with these therapies. However, many questions about infection risk and timing in patients treated with bispecific antibodies for myeloma remain. In addition to better defining how to protect patients from common bacterial and viral infections, possibly with the use of IV immunoglobulin therapy, several specific opportunistic infections would

Notable opportunistic infections reported in patients with multiple myeloma treated with bispecific antibody therapy

Bacterial infections
Salmonellosis
Viral infections
CMV viremia and end-organ disease
Adenovirus pneumonia and hepatitis
Disseminated zoster
JC virus infection causing progressive multifocal leukoencephalopathy
Parvovirus infection
Enterovirus infection
Fungal infections
Pneumocystis jirovecii pneumonia
Invasive aspergillosis
Candida esophagitis
Parasitic infections
Toxoplasmosis

Infections derived from those reported in references 2 and 6-8.

benefit from a detailed study. CMV reactivation is clearly a risk, but when does this risk begin after bispecific antibody therapy is started, and what is the incidence over time? Which patients are at the highest risk, who may benefit from monitoring or prophylaxis, and when should this start? Severe adenovirus infection has been reported in this patient population and is a viral infection without an approved antiviral therapeutic option. What are the risk factors for severe adenovirus infection in patients treated with bispecific antibody therapy, and when is the risk for adenovirus highest relative to when therapy is started? Early identification of infection risk factors coupled with a better understanding of the timing of opportunistic infections would allow for treatment modification to avoid potentially severe complications.

The adoption of this insightful harmonization proposal by Ludwig et al will bring us closer to understanding the dynamic infection risk associated with bispecific antibody therapy for patients with multiple myeloma with attention to the fact that patients can become infected with >1 pathogen and that the infection risk is present throughout therapy. Improved trial reporting on when all infections occur, combined with the information we have learned from post-marketing and single-center studies, will allow us to better understand how to protect patients from common and opportunistic infections while deriving benefits from this effective class of therapy.

Conflict-of-interest disclosure: S.P.H. has received research funding from F2G, GlaxoSmithKline, Scynexis, Cidara Therapeutics, and Mundipharma; and has served as a consultant or adviser for Melinta, Pfizer, Roche, and Seres Therapeutics.

References

1. Ludwig H, Munshi N, Terpos E, et al. Proposal for harmonizing the reporting of infections during treatment with bispecific antibodies in multiple myeloma. *Blood Adv*. 2024;8(18):4979-4982.
2. Nooka AK, Rodriguez C, Mateos MV, et al. Incidence, timing, and management of infections in patients receiving teclistamab for the treatment of relapsed/refractory multiple myeloma in the MajesTEC-1 study. *Cancer*. 2024;130(6):886-900.
3. Cliff ERS, Reynolds G, Popat R, Teh BW, Kesselheim AS, Mohyuddin GR. Acknowledging infection risk in bispecific antibody trials in the treatment of multiple myeloma. *J Clin Oncol*. 2023;41(10):1949-1951.
4. Raje N, Anderson K, Einsele H, et al. Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: consensus recommendations from an expert panel. *Blood Cancer J*. 2023;13(1):116.
5. Mohan M, Chakraborty R, Bal S, et al. Recommendations on prevention of infections during chimeric antigen receptor T-cell and bispecific antibody therapy in multiple myeloma. *Br J Haematol*. 2023;203(5):736-746.
6. 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 Adv*. 2023;7(13):3069-3074.
7. Jourdes A, Cellerin E, Touzeau C, et al. Characteristics and incidence of infections in patients with multiple myeloma treated by bispecific antibodies: a national retrospective study. *Clin Microbiol Infect*. 2024;30(6):764-771.
8. Lancman G, Parsa K, Kotlarz K, et al. IVIg use associated with ten-fold reduction of serious infections in multiple myeloma patients treated with anti-BCMA bispecific antibodies. *Blood Cancer Discov*. 2023;4(6):440-451.
9. Freriches KA, Virkleij CPM, Mateos MV, et al. Teclistamab impairs humoral immunity in patients with heavily pretreated myeloma: importance of immunoglobulin supplementation. *Blood Adv*. 2024;8(1):194-206.

https://doi.org/10.1182/bloodadvances.2024013813