

CORRESPONDENCE OPEN



Adverse effects and non-relapse mortality of BCMA directed T cell therapies in multiple myeloma: an FAERS database study

© The Author(s) 2024

Blood Cancer Journal (2024)14:36; <https://doi.org/10.1038/s41408-024-01023-9>

Dear Editor,

B-cell maturation antigen (BCMA)-directed T cell therapies such as idecabtagene vicleucel (ide-cel), ciltacabtagene autoleucel (cilta-cel), teclistamab, and elranatamab have changed the therapeutic landscape of patients with relapsed/refractory multiple myeloma (MM) [1–4]. Despite their effectiveness, chimeric antigen receptor (CAR) T-cell and bispecific antibody (bsAb) therapies have distinct toxicity profiles, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), non-ICANS neurotoxicity, and the risk of infections, all contributing to significant morbidity and potentially non-relapse mortality (NRM) [1–11]. However, there is substantial variability in attributing treated-related adverse effects and mortality to the therapy in the pivotal registration clinical trials [12]. The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database contains reports of adverse events, medication error, and product quality complaints that were submitted to the FDA. Although healthcare providers and consumers voluntarily contribute to the data source, drug manufacturers are obligated to provide mandatory reporting. Herein, we analyzed the most reported adverse events and NRM among the FDA-approved BCMA-directed immunotherapy in MM.

For this study, we identified reports of adverse effects associated with ide-cel, cilta-cel, and teclistamab from the first quarter of 2019 to the second quarter of 2023. Elranatamab was not included in this analysis due to fewer reported cases ($n = 23$). Reporting odds ratio (ROR) was defined as odds of a reaction in a specific drug divided by the odds of that reaction in all other drugs. Non-relapse mortality was calculated by excluding disease progression from fatal cases. Odds ratio (OR) for mortality was defined as odds of fatal reports in a given drug divided by the odds of fatal reports in other drugs.

After excluding cases involving the use of more than one drug, a total of 1803 individual cases with 4423 adverse effects were identified. Table 1 summarizes the baseline characteristics of patients included. Overall, ide-cel ($n = 584$) and teclistamab ($n = 723$) had the most reported events. Adverse effects leading to hospitalizations were more common with teclistamab (53.5%) and cilta-cel (47.4%) compared to ide-cel (35.6%). Teclistamab demonstrated the highest rates of life-threatening events ($n = 81$; 11.3%) and death ($n = 159$; 22.1%) associated with an adverse effect among the 3 drugs (Table 1).

Next, we specifically investigated the adverse effects of interest, namely CRS, ICANS, non-ICANS neurotoxicity, and infections. The rate of CRS was highest with ide-cel (16.1%), while the reported instances of ICANS were similar between ide-cel (3.8%) and cilta-cel (3.3%). Non-ICANS neurotoxicity was reported with both ide-cel ($n = 215$, 10.1%) and cilta-cel ($n = 56$, 6.4%). Further, we looked into the

most commonly reported attributes of non-ICANS neurotoxicity associated with these agents. Bell's palsy was reported almost exclusively with cilta-cel ($n = 13$, 1.5%), with 1 case reported with teclistamab. Parkinsonism was seen more frequently with cilta-cel ($n = 7$, 0.8%) compared to ide-cel ($n = 4$, 0.2%). Infections such as pneumonia ($n = 63$; 4.6%), sepsis ($n = 33$; 2.4%) and COVID-19 ($n = 39$; 2.8%) were more common with teclistamab. Pneumocystis jirovecii pneumonia ($n = 10$, 0.7%), cytomegalovirus (CMV) reactivation ($n = 9$, 0.7%), and CMV pneumonia ($n = 6$, 0.4%) were also predominantly linked to teclistamab. Ide-cel was associated with 3 cases of multifocal leukoencephalopathy (PML), while none were reported with cilta-cel or teclistamab.

Next, we analyzed ROR for the most frequently reported adverse effects, namely CRS, ICANS, non-ICANS neurotoxicity and infection (Fig. 1A). Ide-cel exhibited the highest ROR for CRS (1.8, 95% CI 1.5–2.16) and non-ICANS neurotoxicity (2.19, 95% CI 1.73–2.77). Whereas for infection, cilta-cel showed a higher ROR (1.3, 95% CI 1.04–1.62) while ide-cel has lower ROR (0.13, 95% CI 0.1–0.17). Notably, teclistamab showed a highest ROR (4.38, 95% CI 3.61–5.31) for infections, but lowest ROR for CRS (0.63, 95% CI 0.51–0.78), ICANS (0.69, 95% CI 0.47–1.02) and non-ICANS neurotoxicity (0.4, 95% CI 0.3–0.54) in comparison to ide-cel and cilta-cel.

We then analyzed the NRM attributed to these agents (Fig. 1B). The OR for NRM was compared between the 3 therapies and showed that ide-cel had the lowest OR (0.53, 95% CI 0.4–0.71) for NRM followed by cilta-cel (OR 0.99, 95% CI 0.75–1.31). Teclistamab exhibited the highest OR (1.72, 95% CI 1.35–2.2) for NRM. The common events in NRM cases related to ide-cel were CRS, ICANS, and sepsis, whereas cilta-cel was associated with CRS, ICANS, and hemophagocytic lymphohistiocytosis (HLH). In NRM cases associated with teclistamab, the most prevalent events were infections including COVID-19, sepsis, and pneumonia.

Overall, our study highlights the distinctive toxicity profile associated with BCMA-directed T cell therapies in MM. We observe the highest rates of life-threatening events, hospitalization, and death with teclistamab compared to ide-cel and cilta-cel. Unlike CAR T-cell therapy with the current vein-to-vein time ranging between 47–71 days, bsAbs are readily available off-the-shelf options for patients with rapidly relapsing disease [13, 14]. Additionally, adequate organ function is prerequisite for CAR T-cell therapy, similar to the requirement for autologous stem cell transplant, inadvertently introducing a selection bias. The increased events and non-relapse mortality with teclistamab could be indicative of this patient population, or, alternatively, may be linked to significant morbidity and mortality linked to infections associated with bsAbs, as previously recognized [9].

The rates of CRS and ICANS were higher with BCMA CAR T-cell therapy compared to teclistamab. The spectrum of non-ICANS neurotoxicity associated with CAR T-cell therapy includes encephalopathy, tremor, aphasia, delirium, Parkinsonism, cranial nerve palsies, and peripheral neuropathies, like previously described occurrences [6]. Ide-cel has the highest ROR for non-ICANS

Received: 20 November 2023 Revised: 26 February 2024 Accepted: 27 February 2024

Published online: 05 March 2024

Table 1. Baseline characteristics and most reported adverse events in BCMA directed immunotherapy in patients with relapsed and/or refractory multiple myeloma.

Characteristic	Ide-cel	Cilta-cel	Teclistamab
Number of patients	584	477	723
Number of adverse events reported	2132	874	1363
Age- yrs. median (interquartile)	66 (58.5–71)	66 (57.8–71)	65 (57–72)
Female (%) ^a	225 (38.5)	117 (24.5)	229 (31.8)
Death (%) ^a	68 (11.6)	82 (17.2)	159 (22.1)
Life threatening (%) ^a	43 (7.4)	42 (8.8)	81 (11.3)
Hospitalization (%) ^a	208 (35.6)	226 (47.4)	385 (53.5)
CRS (%) ^a	344 (16.1)	90 (10.3)	130 (9.5)
ICANS (%) ^a	80 (3.8)	29 (3.3)	34 (2.5)
Non-ICANS neurotoxicity (%) ^a	215 (10.1)	56 (6.4)	52 (3.8)
Pneumonia (%) ^a	4 (0.2)	20 (2.3)	63 (4.6)
Sepsis (%) ^a	15 (0.7)	17 (2.0)	46 (3.4)
COVID-19 infection (%) ^a	4 (0.2)	24 (2.7)	69 (5.0)
Infection (%) ^a	4 (0.2)	2 (0.2)	19 (1.4)

Per 21CFR314.80, Life threatening event are defined as any adverse drug experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse drug experience as it occurred, i.e., it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

^aN (%)

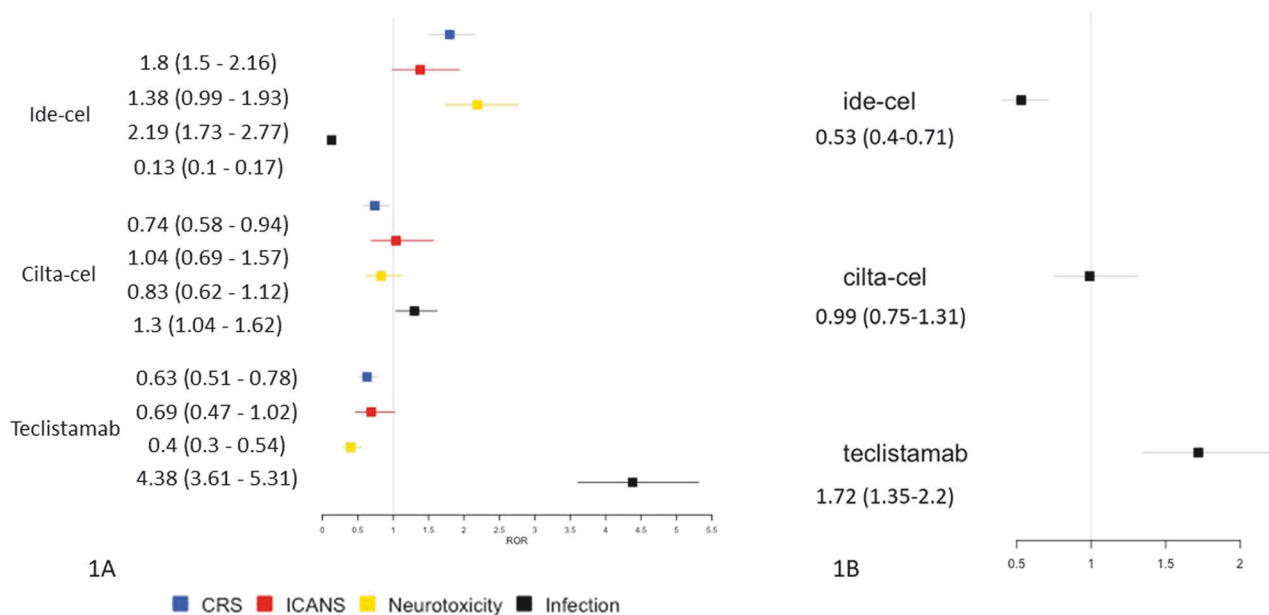


Fig. 1 Forest Plots. A Forest plot of distribution of CRS, ICANS, Non-ICANS neurotoxicity and infection among BCMA directed immunotherapy. **B** Forest plot of the non-relapse mortality among BCMA directed immunotherapy in patients with relapsed and /or refractory multiple myeloma. ROR reporting odds ratio, OR odds ratio, NRM non relapse mortality.

neurotoxicity; however, this should be interpreted with caution due to a relatively larger number of ide-cel cases within the database, reflecting its status as the first FDA-approved BCMA CAR T-cell therapy. Parkinsonism was 4.3 times higher with cilta-cel compared to ide-cel. Bell's palsy was exclusively observed with cilta-cel, with no reported cases associated with ide-cel. Both are consistent with clinical trial data [2].

Teclistamab was associated with a significantly stronger signal of infectious complication compared to ide-cel and cilta-cel, again consistent with current literature [9, 10]. The highest OR for NRM was noted with teclistamab followed by cilta-cel and ide-cel. While the exact attributes of NRM cannot be ascertained from the FAERS database, toxicities of CAR T-cell therapy and infections were the

predominant events associated with NRM. Death unrelated to disease progression were reported with ide-cel in the KarMMA-1, KarMMA-3, and a real-world multi-institutional study and were attributed to complications such as CRS, HLH, neurotoxicity, COVID-19 infection, and cardiomyopathy [1, 8, 15]. The CARTITUDE 1 clinical trial also reported NRM attributed to various causes, including CRS/HLH, neurotoxicity, infections, and AML [2]. A recent study of commercial cilta-cel, reported a NRM of 9% (13/139) related to CRS, ICANS, delayed neurotoxicity and infections [14]. In the CARTITUDE 4 study of cilta-cel, 14% of deaths (25/39) among patients who received CAR T-cell infusion ($n = 176$) were attributed to causes unrelated to disease progression [5]. Similarly, clinical trial of bsAbs also reported cases of NRM related to COVID-19 infection, hepatic

failure, and PML [3, 4]. Collectively, these findings reflect the substantial burden of NRM across various T-cell therapies.

Our analysis is limited by the nature of the FAERS database, where reporting is not mandatory, and selection bias cannot be eliminated. We presume consistent reporting practices for the same adverse events across different agents, ensuring the relevance of utilizing ROR for this analysis. Moreover, the timing of adverse effects, such as infection and NRM can be influenced by duration of treatment and time interval between events, and this data cannot be reliably calculated from the database. Nevertheless, since these agents share a similar indication for MM, clinicians will need to carefully consider their distinct toxicity profiles when choosing and sequencing treatments. Despite these limitations, these data offer a unique opportunity to comprehend adverse effects and NRM attributed to these novel therapies.

Zimu Gong¹, Godsfavour Umoru¹, Jorge Monge²,
Nishi Shah³, Ghulam Rehman Mohyuddin⁴,
Sabarinath Venniyil Radhakrishnan⁵, Rajshekhar Chakraborty⁶,
Leo Rasche⁷, Carolina Schinke⁸, Anita D'Souza⁵ and
Meera Mohan⁵✉

¹Division of Hematology Oncology, Houston Methodist Hospital, Houston, TX, USA. ²Division of Hematology/Oncology, Weill Cornell Medicine, New York, NY, USA. ³Division of Hematological Malignancies, Department of Oncology, Montefiore Medical Center and Albert Einstein College of Medicine, New York, NY, USA. ⁴Division of Hematology/Oncology, University of Utah, Salt Lake City, UT, USA. ⁵Division of Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, USA. ⁶Multiple Myeloma and Amyloidosis Program, Columbia University, Herbert Irving Comprehensive Cancer Center, New York, NY, USA. ⁷Department of Internal Medicine II, University Hospital of Würzburg, Würzburg, Germany. ⁸Myeloma Center, University of Arkansas for Medical Science, Little Rock, AR, USA. This work was partly presented as an oral abstract at the 65th American Society of Hematology Annual Meeting and Exposition, Dec 9-12, 2023, San Diego, California ✉email: memohan@mchw.edu

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

- Munshi NC, Anderson LD Jr, Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med.* 2021;384:705–16.
- Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet.* 2021;398:314–24.
- Moreau P, Garfall AL, van de Donk N, Nahi H, San-Miguel JF, Oriol A, et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med.* 2022;387:495–505.
- Lesokhin AM, Tomasson MH, Arnulf B, Bahls NJ, Miles Prince H, Niesvizky R, et al. Eranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. *Nat Med.* 2023;29:2259–67.
- San-Miguel J, Dhakal B, Yong K, Spencer A, Anguille S, Mateos MV, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N Engl J Med.* 2023;389:335–47.
- Cohen AD, Parekh S, Santomasso BD, Gállego Pérez-Larraya J, van de Donk N, Arnulf B, et al. Incidence and management of CAR-T neurotoxicity in patients with multiple myeloma treated with ciltacabtagene autoleucel in CARTITUDE studies. *Blood Cancer J.* 2022;12:32.
- Van Oekelen O, Aleman A, Upadhyaya B, Schnakenberg S, Madduri D, Gavane S, et al. Neurocognitive and hypokinetic movement disorder with features of parkinsonism after BCMA-targeting CAR-T cell therapy. *Nat Med.* 2021;27:2099–103.

- Rodriguez-Otero P, Ailawadhi S, Arnulf B, Patel K, Cavo M, Nooka AK, et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. *N Engl J Med.* 2023;388:1002–14.
- Mohan M, Nagavally S, Dhakal B, Radhakrishnan SV, Chhabra S, D'Souza A, et al. Risk of infections with B-cell maturation antigen-directed immunotherapy in multiple myeloma. *Blood Adv.* 2022;6:2466–70.
- Hammons L, Szabo A, Janardan A, Bhatlapenumarthy V, Annyapu E, Dhakal B, et al. The changing spectrum of infection with BCMA and GPRC5D targeting bispecific antibody (bsAb) therapy in patients with relapsed refractory multiple myeloma. *Haematologica.* 2024;109:906–14.
- Chari A, Minnema MC, Berdeja JG, Oriol A, van de Donk N, Rodríguez-Otero P, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med.* 2022;387:2232–44.
- 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;41:1949–51.
- Hansen DK, Sidana S, Peres L, Shune L, Sborov DW, Hashmi H, et al. Idecabtagene vicleucel (Ide-cel) chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory multiple myeloma (RRMM): real-world experience. *J Clin Oncol.* 2022;40:8042.
- Hansen D, Patel K, Peres L, Kocoglu M, Shune L, Simmons G, et al. Safety and efficacy of standard of care (SOC) ciltacabtagene autoleucel (Cilta-cel) for relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol.* 2023;41:8012.
- Hansen DK, Sidana S, Peres LC, Leitzinger CC, Shune L, Shrewsbury A, et al. Idecabtagene vicleucel for relapsed/refractory multiple myeloma: real-world experience from the myeloma CAR T consortium. *J Clin Oncol.* 2023;41:2087–97.

ACKNOWLEDGEMENTS

We thank our patients and families for the opportunity to be involved in their care and all the contributions to the advancement in the field. American Society of Hematology Abstract Achievement Award (Z.G.); Advancing a Healthier Wisconsin Endowment-CTSI KL2 award (M.M.).

AUTHOR CONTRIBUTIONS

Conception and design: ZG and MM. Provision of study materials or patients: ZG and MM. Collection and assembly of data: ZG and MM. Data analysis and interpretation: ZG GU, and MM. Manuscript writing: ZG, GU, JM, NS, GRM, SVR, RC, LR, CS, AD, and MM. Final approval of manuscript: all author.

COMPETING INTERESTS

The authors declare that there are no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Meera Mohan.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2024