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Blood 142 (2023) 358–360

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES

Adverse Effects and Non-Relapse Mortality of BCMA-Directed Immunotherapies : An FDA Adverse Event Reporting System (FAERS) Database Study

Zimu Gong, MDPhD[1], Godsfavour Umoru, PharmD[2], Jorge Monge[3], Nishi Shah, MBBS,MPH[4], Ghulam Rehman Mohyuddin, MD[5], Sabarinath Radhakrishnan[6], Rajshekhar Chakraborty, MD[7], Carolina Schinke, MD[8], Anita D'Souza, MDMS[9], Meera Mohan, MD[10]

[1] Cancer Center, Houston Methodist Hospital, Houston, TX
[2] Houston Methodist Hospital, Houston, TX
[3] Weill Cornell Medicine, New York
[4] Department of Oncology, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, NY
[5] Huntsman Cancer Institute, University of Utah, Salt Lake City, UT
[6] Medical college of Wisconsin, Milwaukee, WI
[7] Columbia University Medical Center, New York, NY
[8] Myeloma Center, Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, AR
[9] Medical College of Wisconsin, Milwaukee, WI
[10] BMT and Cellular Therapy Program, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI

Background: The FDA-approved BCMA-directed immunotherapies, which consist of chimeric antigen receptor T (CAR T) cell therapies like idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), alongside the bispecific antibody teclistamab, have improved outcomes for patients with relapsed/refractory multiple myeloma (MM). Despite their effectiveness, these treatments 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 non-relapse mortality. In this study, we analyzed these adverse events using data from the FDA Adverse Event Reporting System (FAERS) database.

Method: We conducted a comprehensive search of the FAERS database from 2019 to 2023 to identify adverse effect reports of interest, associated with ide-cel, cilta-cel, and teclistamab. To ensure data accuracy, we excluded duplicate reports and cases where multiple BCMA-directed agents were associated with a single incident. Reporting odds ratio (ROR) was calculated by dividing the odds of a certain event occurring with the agent by the odds of the same event occurring with all other BCMA agents in the same database. Furthermore, to assess NRM, we excluded reports of progressive or refractory MM from the analysis of fatal cases.

Results: A total of 1314 individual cases, with 3377 reported adverse reactions, were identified. Among them, 353 cases were associated with cilta-cel, 496 with ide-cel, and 465 with teclistamab. The most frequently reported adverse events included CRS at 12.8%, followed by fatigue (3.9%), pyrexia (3.2%), ICANS (3.0%), and non-ICANS neurotoxicity (1.9%). Ide-cel showed the highest ROR for CRS (1.64, 95% CI 1.33-2.02), whereas the ROR for ICANS was lowest with teclistamab (0.55, 95% CI 0.32-0.93). Ide-cel showed the highest ROR for non-ICANS neurotoxicity (2.45, 95% CI: 1.86-3.23). Bell's palsy was exclusively associated with cilta-cel, with 11 reported cases, while Parkinsonism was reported in 6 cases with cilta-cel, 2 cases with ide-cel, and none with teclistamab.Teclistamab had a notably higher proportion of infection-related events, accounting for 23.7% of all reported cases, as compared to 13.7% for cilta-cel and 2.9% for ide-cel. The ROR for infection was highest with teclistamab at 5.21 (95% CI: 4.14 - 6.56). Out of the total reported deaths (n=225 cases), NRM was observed in 189 patients, accounting for 84% of all mortality cases. In the analysis of NRM , ide-cel was associated with 42 reported deaths, with CRS (n=17; 40%), ICANS (n=8; 19%), sepsis (n=7; 17%), and hemophagocytic lymphohistiocytosis (HLH) (n=6; 14%) being the most common reported adverse events in this group. For cilta-cel, 59 deaths were reported, with CRS (n=17; 29%), ICANS (n=13; 22%), and HLH (n=9; 15%) as the most common adverse events in patients who suffered NRM. In the case of teclistamab, among the 88 NRM cases, the most frequent adverse events reported were COVID-19 (11.4%), pneumonia (11.4%), sepsis (9.1%), and septic shock (9.1%). Teclistamab exhibited the highest OR for NRM at 1.73 compared to 1.28 with cilta-cel and 0.42 with ide-cel. The findings will be presented with updated data.

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Conclusion: Our analysis of the FAERS dataset demonstrates a prominent risk of CRS and ICANS with CAR-T therapy, as well as a high risk of infection related mortality with teclistamab. Non-ICANS neurotoxicity was more pronounced with ide-cel compared to cilta-cel, potentially influenced by the longer follow-up period and wider uptake of ide-cel as it was the first FDA-approved CAR T therapy. We also note a higher NRM with both cilta-cel and teclistamab compared to ide-cel. While the exact attributes of NRM cannot be accessed in the database, complications of CAR T therapy and infections were the most common events noted in the group with NRM. Our analysis is limited by the nature of the FAERS database, where reporting is not mandatory, and selection bias cannot be eliminated. Since these agents share a similar indication for MM, clinicians will need to carefully consider their distinct toxicity profiles when choosing and sequencing treatments.

Disclosures Chakraborty: *Sanofi Pasteur:* Consultancy; *Janssen:* Consultancy; *Adaptive Biotechnologies:* Consultancy. **D'Souza:** *Abbvie, BMS, Caelum, Janssen, Novartis, Pfizer, Sanofi, Sorrento, Takeda, Prothena:* Ended employment in the past 24 months, Research Funding. **Mohan:** *Takeda Pharmaceutical Company:* Research Funding; *Ionis Pharmaceuticals:* Research Funding; *GlaxoSmithKline plc:* Research Funding; *Bristol-Myers Squibb Company:* Research Funding; *Celgene Corporation:* Research Funding; *Novartis:* Research Funding; *Amgen Inc:* Research Funding; *Blood Cancer Today:* Honoraria; *MashupMD:* Honoraria; *MJH life sciences:* Honoraria; *Institutional KL2 Award:* Other: Research Grant; *Sanofi S.A:* Consultancy, Research Funding.

https://doi.org/10.1182/blood-2023-182695

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Table 1. Adverse events of BCMA therapeutics

	Cilta-cel	Ide-cel	Teclistamab
Total cases	353	496	465
Total events	626	1847	904
CRS			
N	67 (10.7%)	283 (15.3%)	85 (9.4%)
ROR, 95% CI	0.78 (0.59-1.03)	1.64 (1.33-2.02)	0.63 (0.49-0.81)
ICANS			
N	22 (3.5%)	62 (3.4%)	17 (1.9%)
ROR, 95% CI	1.23 (0.76-1.99)	1.33 (0.89-2)	0.55 (0.32-0.93)
Infection			
N	86 (13.7%)	53 (2.9%)	214 (23.7%)
ROR, 95% CI	1.48 (1.14-1.92)	0.12 (0.09-0.16)	5.21 (4.14-6.56)
Non-ICANS neurotoxicity			
N	37 (5.9%)	202 (10.9%)	36 (4.0%)
ROR, 95% CI	0.66 (0.46-0.94)	2.45 (1.86-3.23)	0.39 (0.27-0.56)
Outcome			
Death	62 (17.6%)	51 (10.3%)	112 (24.1%)
Life threatening	38 (10.8%)	33 (6.7%)	58 (12.5%)
Hospitalization	183 (51.8%)	181 (36.5%)	260 (55.9%)
Non relapse mortality			
N	59 (16.7%)	42 (8.5%)	88 (18.9%)
OR 95% CI	1.28 (0.92-1.79)	0.42 (0.29-0.6)	1.73 (1.27-2.36)

ROR: reporting odds ratio; OR: odds ratio

Figure 1