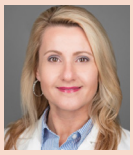
BCMA-Directed CAR T Cells in Relapsed Refractory Multiple Myeloma: Highlights From SOHO 2021



Lisa Nodzon PhD, APRN, AOCNP®, of Moffitt Cancer Center, reviews data on clinical trials and future directions in BCMA-directed CAR T cells presented in a session by Jesus G. Berdeja, MD, of Sarah Cannon Cancer Institute, at the 2021 SOHO Annual Meeting.

B-cell maturation antigen (BCMA)-targeted therapy has become an important treatment consideration for relapsed refractory (R/R) multiple myeloma (MM) patients (Yu et al., 2020). This novel treatment is rapidly emerging due to BCMA's highly selective expression in malignant plasma cells. Several BCMA-targeted agents are currently in active clinical development. Patient education, risk mitigation, BCMA-related toxicity management, and long-term follow-up are important considerations for advanced practitioners when managing patients with R/R MM undergoing this novel treatment.

Updates on both the phase II KarMMa trial and phase Ib/II CARTITUDE-1 study of chimeric antigen receptor (CAR) T cells in heavily pretreated R/R MM were presented during the ninth annual Society of Hematologic Oncology meeting (Berdeja et al., 2021; Munshi et al., 2021).

IDECABTAGENE VICLEUCEL

The phase II KarMMa trial utilized idecabtagene vicleucel (ide-cel), which is an autologous CAR T product that showed efficacy in high-risk heavily pretreated R/R MM patients, with an overall response rate (ORR) of 73% with 33% complete response (CR) and time to first response of 1 month (Munshi et al., 2021). Higher doses were associated with higher expansion and better responses. Minimal residual disease negativity was observed in 79% of patients with ≥ CR. Median progression-free survival (PFS) was 8.6 months, with median overall survival (OS) of 24 months. Progression-free survival was dose dependent and improved with depth of response.

Most common adverse events were as expected for CAR T-cell therapy, with grade ≥ 3 cytopenias, any-grade cytokine release syndrome (CRS) of 84% with time to onset of 1 day, and any-grade neurotoxicity of 18% with time to onset of 2 days. Tocilizumab and steroids were used to manage patients with CRS in 52% and 15%, respectively.

Key Points

- Prompt recognition and management of CRS and neurotoxicity in patients on CAR T-cell therapy is essential for optimizing outcomes.
- Myelosuppression is a very common toxicity that can persist, and therefore requires ongoing monitoring as well as supportive management for patients.
- Due to the high risk for infection, prophylactic antimicrobials should be employed in a patient-dependent manner.

J Adv Pract Oncol 2022;13(suppl 1):23–25
https://doi.org/10.6004/jadpro.2022.13.1.15

CILTACABTAGENE AUTOLEUCEL

In CARTITUDE-1, the ciltacabtagene autoleucel (cilta-cel) construct differed from ide-cel by containing two BCMA-targeting binding domains designed to confer greater avidity (Berdeja et al., 2021). Like the KarMMa trial, this study included high-risk heavily pretreated R/R MM patients receiving at least ≥ 3 prior therapies. Cilta-cel demonstrated an impressive ORR of 97%, CR rate of 67%, and very good partial response (VGPR) of 94%. Twelve-month PFS was 77%.

Grade ≥ 3 cytopenias were observed, with neutropenia predominating at 95%. Any-grade diarrhea (29%) and nausea (27%) occurred. Cytokine release syndrome of any grade was observed in 95%, with grade ≥ 3 at 5%; however, time to onset was 7 days and any-grade neurotoxicity of 20%. Cytokine release syndrome events were manageable with tocilizumab or corticosteroids. A delay in neurotoxicity was observed at day 27 and associated with parkinsonian-type movements and focal cranial nerve findings; therefore, mitigation factors were enacted for patients with two or more higher risk factors such as high tumor burden, grade ≥ 2 CRS, high CAR T-cell expansion, or immune effector cell–associated neurotoxicity (ICANS). Such patients underwent bridging therapy to reduce tumor burden with early and aggressive treatment of CRS and ICANS.

At present, only ide-cel has been U.S. Food and Drug Administration (FDA) approved for R/R MM in those receiving at least ≥ 4 lines of therapy, with pending approval for cilta-cel. Given the activity of these constructs in R/R MM, additional versions of the KarMMa and CARTITUDE trials are underway looking at CAR T-cell therapy in earlier lines of treatment, including front line.

IMPROVEMENTS IN CAR T-CELL THERAPY

Despite promising results of these trials, there is need for product improvement, with novel products in development as relapses occur (D'Agostino & Raje, 2019; Yu et al., 2020). This unmet need is due to downregulation or loss of BCMA expression, upregulation of resistant mechanisms in the tumor cell and tumor microenvironment, or loss or quality of CAR T cells. Therefore, potential future explorations include alternate antigen targets beyond BCMA and off-the-shelf products.

Novel products are currently under investigation to overcome the deficits and challenges of these early CAR T-cell products (Yu et al., 2020). ALLO-715, the first genetically modified BCMA AlloCART cell product, is being explored in the UNIVERSAL phase I trial for R/R MM with ≥ 3 prior lines of therapy including an immunomodulatory agent, proteasome inhibitor, and anti-CD38 therapy (Mailankody et al., 2020). Most common grade ≥ 3 adverse events include anemia (41%), neutropenia (41%), and thrombocytopenia (29%). No neurotoxicity or graft-vs.-host disease has been reported, while all grades of CRS have been observed in 45% of patients.

Advantages with ALLO-715 over ide-cel and cilta-cel are that no bridging therapy is required, and patients are ready for therapy within 5 days of study enrollment (Berdeja et al., 2021; Mailankody et al., 2020). Infection rates were like those seen in other studies for R/R MM. While early, the data show a manageable safety profile with clinical activity for patients with R/R MM and that higher cell doses are associated with greater activity.

The Advanced Practitioner Perspective

Advanced practitioners should be aware that CAR T-cell therapy is now FDA approved for R/R MM. Prompt recognition and management of treatment-related adverse events is characteristic of this treatment modality. Early management of CRS and neurotoxicity is critical for optimizing patient outcomes. Myelosuppression is a common toxicity in CAR T-cell therapy that can persist for months following infusion, increasing the risk for infectious complications. Such patients require ongoing monitoring and supportive antimicrobial management until hematologic recovery.

Disclosure

Dr. Nodzon has served on the speakers bureaus for AbbVie and Genentech and as a consultant for AbbVie, AstraZeneca, Genentech, Pharmacyclics, and Takeda.

References

Berdeja, J. G., Madduri, D., Usmani, S. Z., Jakubowiak, A., Agha, M., Cohen, A. D.,...Banerjee, A. (2021). 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*, *398*(10297), 314–324. https://doi.org/10.1016/s0140-6736(21)00933-8

D'Agostino, M., & Raje, N. (2019). Anti-BCMA CAR T-cell therapy in multiple myeloma: Can we do better? *Leukemia*, *34*(1), 21–34. https://doi.org/10.1038/s41375-019-0669-4

Mailankody, S., Matous, J. V., Liedtke, M., Sidana, S., Malik, S., Nath, R.,...Hari, P. (2020). 129 Universal: An allogeneic first-in-human study of the anti-Bcma ALLO-715 and the anti-CD52 ALLO-647 in relapsed/refractory multiple myeloma Oral abstract #129. 62nd ASH Annual Meeting and Exposition; Dec 5, 2020; Virtual.

Munshi, N. C., Anderson, L. D., Shah, N., Madduri, D., Berdeja, J., Lonial, S.,...Petrocca, F. (2021). Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *New England Journal of Medicine*, *384*(8), 705–716. https://doi.org/10.1056/nejmoa2024850

Yu, B., Jiang, T., & Liu, D. (2020). BCMA-targeted immunotherapy for multiple myeloma. *Journal of Hematology & Oncology*, *13*(1), 125. https://doi.org/10.1186/s13045-020-00962-7