COMPLETE RESPONSE IN HEAVILY PRETREATED REFRACTORY MANTLE CELL LYMPHOMA AFTER BENDAMUSTINE AND GLOFITAMAB: A PARADIGM SHIFT IN IMMUNOTHERAPY SEQUENCING

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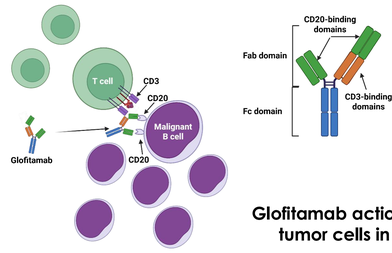
Context

Mantle cell lymphoma (MCL) is a rare and aggressive subtype of non-Hodgkin lymphoma characterized by frequent relapses and poor prognosis, particularly in the relapsed/refractory (R/R) setting. Standard therapeutic options, including BTKi and BCL2 inhibitors, often yield diminishing response durations with each line of therapy. Thus, bispecific T-cell engager antibodies like **Glofitamab** (a CD20 X CD3 bispecific antibody) emerged as promising agents.

Although Glofitamab administration after **Bendamustine** is generally not recommended, due to its profound and prolonged T-cell depletion, which impairs the immune activation mechanism critical for bispecific antibody efficacy, this clinical report aims to call attention to a noteworthy case of complete metabolic remission achieved with Glofitamab in a patient with heavily pretreated MCL who received Bendamustine immediately prior to Glofitamab initiation, challenging current paradigms in immunotherapy sequencing.

Patient

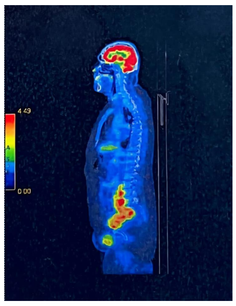
A 64-year-old male presented with advanced-stage MCL, confirmed through colon and tonsil biopsies, with a low proliferative index (Ki-67 < 10%) at diagnosis. The disease was extensive, involving supradiaphragmatic and mesenteric lymph nodes, with stage IVB classification and a high-risk MIPI score.



Glofitamab action on tumor cells in MCL

Results

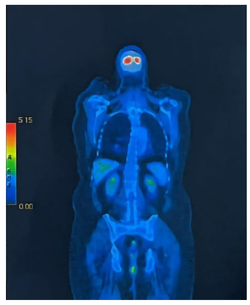
First-Line Therapy: Six R-CHOP/R-DHAP cycles, followed by disease progression.
Second-Line Therapy: Ibrutinib, with transient disease control and subsequent progression after two years.
Third-Line Therapy: Venetoclax, maintaining stability for two years before progression.
Evolution: A biopsy at progression revealed high proliferative MCL (Ki-67 > 50%) with aberrant MUM1 expression.
PET-CT showed extensive nodal disease, splenic involvement, and a partially stenosing cecal tumor mass.

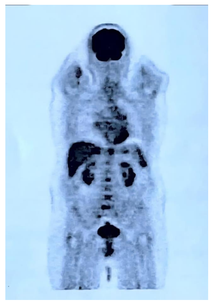



After R-CHOP/R-DHAP, Ibrutinib, Venetoclax



After R-BAC





After Glofitamab

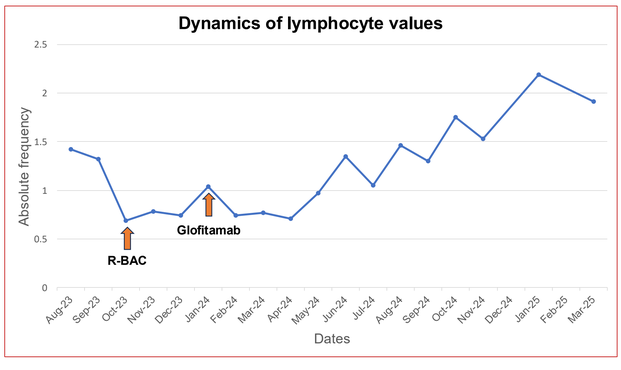
Discussion

The patient received the R-BAC regimen as salvage therapy, achieving partial metabolic response. However, the patient was ineligible for autologous stem cell transplantation.

Despite the known immunosuppressive effects of Bendamustine, which include long-term T-cell depletion and functional impairment, the patient was enrolled in a compassionate use program for Glofitamab due to the absence of other viable options.

Glofitamab was administered as a fixed-duration therapy with a step-up dosing strategy to minimize CRS, with Obinutuzumab preconditioning to mitigate adverse effects.

Remarkably, the patient achieved complete metabolic remission on PET-CT after completing 12 cycles of Glofitamab. This outcome was unexpected, given the standard contraindication of administering Glofitamab post-Bendamustine.



Several hypotheses may explain this response:

- **T-cell recovery dynamics:** The patient may have experienced a faster-than-expected recovery of functional T cells, potentially due to individual variations in immune recovery.
- **Functional T-cell reservoirs:** Despite quantitative T-cell depletion, residual T cells may have retained sufficient functionality to be effectively engaged by Glofitamab.
- **Immunomodulatory effects:** Bendamustine has been reported to modulate the tumor microenvironment, potentially enhancing the T-cell activation and cytotoxicity facilitated by Glofitamab.
- **Timing and sequencing:** The short interval between Bendamustine and Glofitamab administration might have allowed sufficient immune recovery while maintaining effective tumor debulking, thus optimizing the conditions for Glofitamab action.

Conclusions

This report highlights a complete response to Glofitamab in a heavily pretreated MCL case following Bendamustine administration, challenging the existing paradigm.

Individualized assessment of T-cell recovery dynamics could allow for more flexible immunotherapy sequencing.

The clinical outcome showcases Glofitamab's potential to reshape high-risk MCL's treatment landscape, emphasizing the need for prospective studies to elucidate the immunological mechanisms enabling effective T-cell engagement post-Bendamustine and to explore optimized bispecific antibodies sequencing strategies in R/R MCL.

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