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Monoclonal Gammopathies & Multiple Myeloma

TARGETING GLUTAMINE METABOLISM POTENTIATES T CELL ENGAGER–MEDIATED IMMUNOTHERAPY IN MULTIPLE MYELOMA

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Introduction: Despite the introduction of novel immunotherapeutic agents, such as CAR-T cells and T cell engagers (TCE), multiple myeloma (MM) remains an incurable disease with frequent relapse and immune evasion. MM cells exhibit a marked dependence on extracellular glutamine (Gln) to sustain anabolic growth, survival, and redox balance, due to the absence of Gln synthetase and high glutaminase (GLS) expression. This reliance establishes a competitive metabolic microenvironment within the bone marrow (BM) niche, where plasma cells (PCs) deplete Gln and limit its availability to immune cells. Conversely, activated T cells, although Gln-dependent, retain metabolic flexibility and can use alternative substrates under Gln restriction. We aimed to explore how altered Gln metabolism impacts immunotherapy response to BCMA/CD3 TCE. We hypothesized that targeting Gln metabolism may increase MM susceptibility to T cell-mediated cytotoxicity while maintaining T cell effector function.
Methods: We investigated the effects of Gln restriction or pharmacological modulation on elranatamab activity, a clinically available BCMA/CD3 TCE. BCMA expression was assessed in human myeloma cell lines (HMCLs) and $CD138^+$ PCs from 29 MM patients, via flow cytometry. Cytotoxicity and T cell activation (CD69, CD25) were assessed both in co-cultures of $BCMA^+$ HMCLs with healthy donor T cells (E:T = 5:1) and in BM mononuclear cells (MNCs) from MM patients. Gln restriction was achieved by culturing HMCLs and BM MNCs in media containing 0.5 mM and 0.2 mM Gln, respectively, for 48 and 72 hours. GLS inhibition was tested using the CB-839 at 0.5 µM for HMCLs and 10 µM for BM MNCs.
Results: Elranatamab elicited potent and antigen-specific cytotoxicity against HMCLs and primary MM cells, accompanied by robust T cell activation. Gln restriction did not reduce TCE-mediated cytotoxicity against HMCLs, which remained comparable to Gln standard conditions. Concurrently, T cell activation was unaffected, indicating a preserved effector functionality. Combined treatment with elranatamab and CB-839 significantly enhanced anti-MM cytotoxic activity compared with either agent alone, without impairing T cell activation. Extending to a more complex *ex vivo* setting, BM MNCs from six MM patients showed that Gln restriction significantly enhanced elranatamab-mediated cytotoxicity, while T cell activation remained preserved or even increased. Notably, all patient-derived samples responded more effectively to elranatamab under Gln-limited conditions, including those poorly or non-responsive in Gln standard medium. Finally, preliminary data indicate that combining elranatamab with CB-839 further enhances tumor cell lysis of primary MM cells, recapitulating the cell line findings.
Conclusions: Collectively, these data suggest a novel rationale to integrate GLS inhibition with BCMA/CD3 TCE as a strategy to overcome metabolic immunosuppression and enhance immunotherapeutic responses in MM patients.