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In which WM patients is CAR-T cell therapy appropriate?

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Waldenstrom Macroglobulinemia (WM) is an indolent B cell lymphoma derived from mature B cells with lymphoplasmacytic phenotype and the ability to secrete monoclonal immunoglobulins (Ig), typically IgM. With the approval of the oral Bruton tyrosine kinase inhibitor, ibrutinib, as single agent or in combination with rituximab, many patients with WM, can achieve years of disease control with minimal toxicity. However, patients who develop either resistance or intolerance to ibrutinib or fail multiple lines of therapy, including chemo-immunotherapy and novel agents, have few options and might benefit from chimeric antigen receptor (CAR)-modified T cells therapy.

CAR T cell constructs are composed of an extracellular domain containing an antibody fragment that recognizes a tumor-associated antigen, fused to signaling domains that activate T cells upon binding. This permits T cells to recognize tumor-associated extracellular antigens in an MHC-independent fashion.

CD19, which is displayed on both normal B cells and in malignant B cell lymphomas and leukemia at high levels, has been the most clinically successful target antigen. CAR technology has been enhanced by the development of second generation CARs which contain the CD3 signaling domain and a co-stimulatory signaling domain, and third generation CARs containing CD3 and the co-stimulatory domain plus a third, independently expressed signal (such as 4-1BB or IL-12) that can serve as an independent ligand or be secreted near the T cell-cancer cell synapse, leading to robust activation.

We have demonstrated that the human WM cell line BCWM.1 is highly susceptible, *in vitro*, to killing by CD19-targeted CAR T cells, but not by mock CAR T cells. Mice injected with BCWM.1 and subsequently treated with a single dose of CD19 CAR T cells, have a highly significant survival advantage compared to mice treated with unrelated CAR T cells.

We have treated three WM patients with CD-19 CAR T cells, the first two with a second generation CAR, the third with a third generation construct. All patients responded with minimal toxicities (all three patients developed grade 1 cytokine release syndrome and one developed grade 1 neurotoxicity). Kinetics of biochemical, nodal and marrow response, data on persistence and expansion of CAR T cells and on cytokine release over time in the peripheral blood will be presented in detail.