DEVELOPMENT OF BCMA-TARGETED IMMUNOTHERAPY USING VACCINE-INDUCED ANTIGEN-SPECIFIC MEMORY CD8+ T CELLS FOR TREATING PATIENTS WITH MULTIPLE MYELOMA

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Background Multiple myeloma (MM) is a largely incurable cancer of the plasma cells. Despite remarkable recent advances in treatment using novel therapeutics, MM remains incurable. Previously, we reported a vaccination strategy that induced antigen-specific memory CD8+ T lymphocytes (CTL) against XBP1 (X-box binding protein 1), CD138 (Syndecan-1) and CS1 (SLAMF7), which are highly expressed in MM cells. Clinical trials on patients with smoldering MM have proven this multi-peptide vaccine’s safety and immunogenicity, and larger clinical trials are ongoing. We further developed a translational research strategy to combine vaccination with the ex vivo expansion and infusion of vaccine-induced antigen-specific memory T cells. As a first step, we focused on targeting the B cell maturation antigen (BCMA), as it is specifically and highly expressed on the MM cells, and developed a protocol to efficiently isolate and expand BCMA-specific memory CTL ex vivo.

Methods In conjunction with our proposed immunogenic heteroclitic BCMA peptide-based vaccine, we have developed a protocol to efficiently isolate and expand the antigen-specific memory CD8+ CTL ex vivo as a supplemental immunotherapy against MM.

Results We developed a feasible and efficient method to secure antigen-specific T cells following the induction of MM-specific CTL using immunogenic heteroclitic BCMA72-80 (YLMFLLRKI) peptide. The resulting CD8+ CTL show specific upregulation of various costimulatory molecules including CD28, 4-1BB, CD40L and OX40. Among the different conditions we evaluated, anti-CD3/CD28 (clinical grade) stimulation produced the greatest expansion of BCMA-specific CTL within 2 weeks and specifically induced the proliferation of antigen-specific central memory CTL (47% with anti-CD3/CD28 treatment vs. 6% without anti-CD3/CD28). To further enhance the efficacy of the final cell product, functionally active BCMA-specific IFN-g+ CTL were sorted and expanded with anti-CD3/CD28, IL-2 (200 units/ml) and IL-15 (10 ng/ml). Under the conditions, we found a significant and continuous expansion (day 3: 2-fold, day 14: 22-fold, day 21: 55-fold) of BCMA-specific CTL with high Th1 cytokine (IL-2, TNF-a) production and anti-tumor activity (CD107a upregulation) against MM, which were both the BCMA epitope-specific and HLA-A2-restricted.

Conclusions BCMA-specific CD8+ CTL can be effectively expanded using clinical grade anti-CD3/CD28 and IL-2/IL-15 to yield MM-specific memory CTL with robust poly-functional anti-tumor activities. These results provide the framework for combining BCMA-peptide vaccination and the specific cellular therapy using the vaccine-induced IFN-g+ memory T cells to further enhance anti-MM immunity and improve MM patient outcome.