RAPID CYTOKINE RELEASE SYNDROME CAUSED BY SHORT-TERM CAR T CELLS IN A PRECLINICAL MOUSE MODEL

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Background Cytokine release syndrome (CRS) is a serious concern in chimeric antigen receptor (CAR) T cell therapy. Rapidly produced CAR T cells are a new format for which CRS occurrence is so far hardly studied. Animal models are needed. Here, we investigate the relationship between short-term CAR T (stCART) and the occurrence of CRS using NSG-SGM3 mice.

Methods In three different setting, the stCART cell potency of triggering CRS was investigated. First, CD19-specific stCART cells were compared to activated PBMC in CD19+ tumor engrafted NSG-SGM3 mice. Second, stCART were administered together with monocytes and compared to conventional CAR T cell plus/minus monocytes into tumor bearing mice. In an extra control group stCAR T cells were infused into naïve mice. Third, stCAR T cell and conventional CAR T cells were compared in naïve mice. Upon applying the cell products, we closely monitored health conditions including appearance, cage activity, and body weight and temperature. Human and murine cytokines were quantified by multiplex bead-based methods in plasma at termination time point.

Results Close inspection of health condition post cell product application revealed in all settings that stCART cell receiving mice developed severe CRS symptoms including significant weight loss and temperature drop within hours after administration. Increased levels of pro-inflammatory cytokines appeared especially in presence of monocytes, particularly human IL-2 in the stCART cell group, which was 2-fold increased over the conventional CAR T cell group. Moreover, human IL-6, IL-10, TNF-α, and IFN-γ as well as certain murine cytokines were increased. Interestingly, tumor-free mice having received stCART cells showed not only the worst physiological health status but also the highest levels of cytokine secretion. Importantly, conventional CAR T cells did not induce any symptoms or cytokines under these experimental conditions.

Conclusions Here we present a novel animal model providing insights into side-effects induced by rapidly produced CAR T cells. The findings suggest an increased risk of CRS associated with accelerated manufacturing processes, highlighting the need for further research and improvements in CAR T cell manufacturing techniques to ensure the safety and effectiveness of immunotherapy.

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