Establishing a Preclinical Model to Predict and Mitigate CAR T Cell Toxicity in Prostate Cancer

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Background

Metastatic castration-resistant prostate cancer (mCRPC) represents the most lethal stage of advanced prostate cancer, often resistant to standard therapies, including immune therapies like checkpoint inhibitors. Chimeric antigen receptor (CAR) T cell therapy has shown promise in treating mCRPC, yet significant challenges remain. Prostate-specific membrane antigen (PSMA), a validated CAR T cell target, is expressed not only on mCRPC but also on essential normal tissues, resulting in on-target/off-tumor toxicities that limit the therapeutic index of PSMA-targeted CAR T cells. Recently, a first-in-human phase 1 clinical trial (NCT03089203) conducted by our clinical partners at Penn evaluated the safety and effectiveness of PSMA-targeted CAR T cells in mCRPC patients. While the trial showed encouraging dose-dependent efficacy, treatment response was strongly linked to increased toxicities such as cytokine release syndrome (CRS), macrophage activation syndrome (MAS, also known as immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome or IEC-HS), and immune effector cell-associated neurotoxicity syndrome (ICANS). Similar toxicities were reported in a separate phase 1 multi-center trial (Tm-PSMA-01; NCT04227275) evaluating PSMA-targeted CAR T cells in advanced mCRPC.

Methods

Given that human PSMA (huPSMA) surface expression is not restricted to the prostate, we developed a physiologically relevant, immunocompetent mouse model to study on-target/off-tumor toxicities of huPSMA-targeted therapies. Using huPSMA knock-in (KI) mice from Biocytogen, we established a colony in which huPSMA expression is regulated by the mouse PSMA promoter. These huPSMA-KI mice allow for the assessment of toxicities in a context that mimics human physiology.

Results

Initial characterization of the huPSMA-KI mice revealed high huPSMA expression in the kidneys, with ongoing studies assessing expression in other organs. Using this model, PSMA-targeted CAR T cell therapy induced significant toxicity, with lethality occurring as early as day five post-treatment. A full veterinary histopathological examination correlated neurotoxicity and myeloid hyperplasia as probable causes of death. This was evidenced by the necrotic and degenerative changes in the brain and spinal cord, as well as myeloid hyperplasia in the bone marrow. These observed lethal toxicities closely mirror the ICANS and MAS (IEC-HS) observed in clinical trials with PSMA-targeted therapies.

Conclusions

Our study highlights the huPSMA-KI mouse model as a critical tool for assessing the on-target/off-tumor toxicity of PSMA-targeting therapies. By accurately recapitulating human toxicities, this model serves as a platform for preclinical testing to improve the safety and efficacy of CAR T cell therapies for mCRPC. It has the potential to guide the design of safer, more effective clinical trials for mCRPC, ultimately improving patient outcomes and quality of life by minimizing life-threatening toxicities.

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Conflicts of Interest Disclosure Statement

The authors declare no conflict of interest.