SYSTEMIC DISTRIBUTION OF GAMMA-DELTA PSCA-CAR T CELLS IN COMBINATION WITH ZOLEDRONATE IN A MODEL OF BONE METASTATIC PROSTATE CANCER

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Background Metastatic castrate resistant prostate cancer (mCRPC) frequently manifests in the bone, leading to increased morbidity and mortality. We have previously demonstrated that gd Chimeric Antigen Receptor (CAR) T cells targeting prostate stem cell antigen (PSCA) led to significant regression of established prostate cancer cells in the bone. Regression was further increased by combination with the bisphosphonate zoledronate (ZOL), usually administered to mCRPC patients to skeletal related events. To further optimize the use of gd CAR T cells for mCRPC, we aimed to determine the kinetics of gd CAR T cell accumulation and activation in a mouse model of bone metastatic prostate cancer, either as single treatment or in combination with ZOL.

Methods Male NSG mice were intratibial injected with C4-2B prostate cancer cells expressing PSCA and luciferase with the contralateral tibia receiving PBS. ZOL (25 ug/kg) was injected every other day subcutaneously in half of the mice and was discontinued one day prior to administering T cells. When tumors were established, mice received gd PSCA-CAR T cells, gd untransduced (UT) T cells or were left untreated. Bone marrow from tumor-bearing or naive tibias, femur, spleen and blood were recovered at multiple time points, and the number of gd T cells and their activation status were analyzed by flow cytometry.

Results gd CAR T cells showed an accumulation in the bone marrow recovered from tumor-bearing tibias, with 3 times more gd T cells detected compared to mice treated with gd UT cells (p=0.0002). The number of gd T cells peaked at 5 days post infusion and could still be detected after 21 days. Increased gd CAR T cell accumulation was not observed in tumor naive bone marrows, spleen or blood, suggesting a preferential localization of gd CAR T cells at tumor sites. Moreover, gd CAR T cells presented increased expression of CD25, PD1 and CD56 in comparison with gd UT after only 5 days (p<0.001) suggesting their enhance activation. Treatment with ZOL did not significantly affect the number of gd T cells accumulated in bone.

Conclusions gd PSCA-CAR T cells quickly accumulate and become activated at tumor sites with limited distribution outside the bone. ZOL does not appear to impact gd PSCA-CAR T distribution kinetics. Taken together, our data further support the suitability for treatment of bone metastasis.

Ethics Approval The study was approved by University of South Florida IACUC, approval number R7429.