SINGLE DOSE PEMBROLIZUMAB IN MURINE CANCER-CACHEXIA MODELS REPLICATES ELEVATED CATABOLIC PEMBROLIZUMAB CLEARANCE IN HUMANS

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Immune checkpoint inhibitor (ICI) monoclonal antibody (mAb) therapies have demonstrated remarkable activity in patients with a variety of solid tumor malignancies over the past decade [1]. Despite many patients achieving durable responses, overall response rates remain low (~30%). Recent retrospective analyses of ICI clinical pharmacology data revealed high baseline ICI clearance (CL) and steady or increasing ICI CL over time are associated with shorter overall survival. Surprisingly, associations between poor response and elevated CL are decoupled from circulating drug levels and receptor occupancy suggesting elevated CL is a biomarker for and not a cause of poor response. In several diseases and with multiple ICIs, high mAb clearance and shorter survival are also associated with classical clinical features of cancer cachexia including increased weight loss and reduced serum albumin levels [2-6]. As these relationships linking ICI mAb clearance, cancer cachexia, and response represent a potential key to understanding resistance to ICI therapy, we sought to determine if the observed increases in ICI mAb clearance in patients could be replicated in immune competent murine models of cancer wasting. Our results demonstrated cachectic mice with both Lewis lung carcinoma (LLC) and colon-26 (C26) allografted tumors do in fact display altered pharmacokinetics of anti-PD1 mAbs. These effects were shown to be cachexia dependent by the inclusion of MC-38 tumor bearing mice that did not develop cachexia and did not exhibit altered anti-PDA mAb pharmacokinetics. Non-linear mixed effects modeling identified presence of tumor, mouse strain, and terminal gastrocnemius muscle weight as significant covariates on CL, and strain as a significant factor on central volume of distribution. Furthermore, hepatic mRNA expression of the neonatal Fc receptor (FcRn), responsible for prolonging circulation of endogenous IgG species and therapeutic IgG mAbs, was downregulated in cachectic mice. In conclusion, our results demonstrated the potential utility of immune competent murine tumor models for studying mechanisms linking cachexia, ICI clearance and response to ICI therapy. Further characterization of FcRn expression in other tissues and in immune cells is ongoing, as FcRn activity in specific immune cell subsets is vital to anti-tumor T-cell response, supporting a possible mechanistic link between cachexia-mediated changes in mAb PK and resistance to ICI therapy.

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