**USE OF MIXED-EFFECTS MODELING TO DEFINE CACHEXIA AND ITS IMPACT ON IMMUNE CHECKPOINT INHIBITOR DISPOSITION IN MURINE CANCER MODELS**

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Recent clinical pharmacology studies have revealed that elevated clearance (CL) of monoclonal antibody (mAb) immune checkpoint inhibitor (ICI) therapies was associated with shorter overall survival (OS) in patients with solid tumors and evidence of cancer-associated cachexia. Turner et al. (2018) presented their analysis of OS for pembrolizumab-treated patients in advanced melanoma and non-small cell lung cancer (NSCLC), and they found that subjects with high pembrolizumab baseline clearance (CL0) had cachexia-related factors and showed decreased OS. Interestingly, the decreased OS was independent to pembrolizumab dose and exposure. Our group recently demonstrated elevated CL of the PD-1-targeted ICI, pembrolizumab, could be replicated in the murine C26 and LLC models of cancer-associated cachexia (Castillo et al., 2021), though elevated pembrolizumab CL was not observed in the non-cachectic MC38 tumor model. Though there are clinical factors (involuntary body weight loss, muscle and fat loss) and biomarkers (e.g. reduced serum albumin) associated with cachexia, there remains a poor understanding of the factors driving cachexia in patients and in animal models. Therefore, our goal is to understand the underlying mechanisms linking mAb ICI CL, anti-tumor efficacy, and cachexia, and we have sought to establish an objective measure of cachexia in our murine models. The aim of this study was to develop a mixed-effects pharmacokinetic (PK) model which can explain the difference in pembrolizumab CL between cachectic (colon carcinoma, C26; Lewis lung carcinoma, LLC), and non-cachectic (colon adenocarcinoma, MC38) mouse models. The model was able to predict pembrolizumab PK in individual mice, and it incorporated several covariates: murine IgG concentration, terminal fat weight, and Fcgrt expression. Moreover, the model was capable of explaining elevated pembrolizumab CL in the two cachectic cancer models (C26 and LLC) versus the tumor-free and the non-cachectic cancer model (MC38). This demonstrated the modeling approach serves as a means to identify factors impacting ICI mAb CL and may also enable a novel, objective definition of cachexia in mice.

Reference

1. Turner DC, Kondic AG, Anderson KM, et al. Pembrolizumab Exposure–Response Assessments Challenged by Association of Cancer Cachexia and Catabolic Clearance. Clin Cancer Res. 2018;24(23):5841-5849.
2. Castillo AM, Vu TT, Liva SG et al. Single-dose pembrolizumab in murine cancer-cachexia models replicates elevated catabolic pembrolizumab clearance in humans. JCSM Rapid Communications. doi: 10.1002/rco2.32 (Article in press)