572 GUT MICROBIOTA TUNING PROMOTES TUMOR-ASSOCIATED ANTIGEN CROSS-PRESENTATION AND ENHANCES CAR T ANTITUMOR EFFECTS

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Background CAR T cell therapy has shown impressive clinical responses in B cell lymphoma and leukemia, and to date, four CAR T therapies targeting CD19 have been approved by the Food and Drug Administration for the treatment of CD19-positive hematologic malignancies. Notwithstanding the encouraging results, a significant proportion of patients experience a lack of response or disease relapse. Recently several studies have shown the influence of commensal microbes on T cell function, specifically in the setting of checkpoint immunotherapy. We previously reported that gut microbiota perturbation by oral vancomycin, affects dendritic cell antigen presentation and cytokine secretion profile and affects the outcome of radiation and CAR-T therapies. Based on these data, in the present study we explore how modulation of the gut microbiota by vancomycin would influence the outcome of CART-19 therapy.

Methods We employed two murine tumor models, the hematopoietic CD19+ A20 lymphoma and the CD19+ B16 melanoma. We injected BALB/c or C57/black6 mice subcutaneously with $2x10^6$ A20 or $1x10^5$ CD19 positive B16 tumor cells. The same day we started treatment with oral vancomycin. Nineteen days after A20 inoculation or eleven days after CD19+ B16, mice were lymphodepletion with total body radiation (TBI). Two days later, CART-19 cells containing second generation fully murine CAR with a 4-1BB costimulatory domain were infused by tail vein. To validate the data in humans, we proceeded by: a. generating "human gut microbiota avatars", antibiotics preconditioned recipient mice were engrafted with human gut microbiota and enrolled in similar experiments mentioned before, and b. evaluating CART-19 peak expansion on lymphoblastic leukemia patients receiving vancomycin.

Results In both models, mice receiving vancomycin in combination with CD19 directed CAR T cell therapy displayed increased tumor-associated antigens (TAAs) presentation and tumor control compared to CART-19 alone. Fecal microbiota transplant from human healthy donors to pre-conditioned mice recapitulated the results obtained in naïve gut microbiota mice. Lastly, B-cell acute lymphoblastic leukemia patients treated with CART-19 and exposed to oral vancomycin showed higher CART-19 peak expansion compared with matched unexposed patients.

Conclusions These results highlight the role of the gut microbiota on immunotherapy and suggest that the modulation of the gut microbiota using vancomycin affects the outcome of CAR T cell therapy.

Trial Registration NCT02030847

Ethics Approval This study was approved by the Internal Review Board at the Hospital of the University of Pennsylvania.

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