METHODS/STUDY POPULATION: This IRB-approved, retrospective study includes patients with SCD treated at Children's Healthcare of Atlanta. Cases underwent HCT between 2010 and 2016. They were randomly matched with 2 patients with SCD who did not undergo HCT. Match criteria included age, sex, disease genotype, and disease severity, which was determined by the number of hospitalizations in the 5 years pre-HCT, prior intensive care unit admission, and prior chronic transfusion therapy. Data extracted included SCD treatment, hospitalizations, emergency department visits, and organ function pre-HCT and 1-, 2-, 3-, and 5-years post-HCT. Organ-specific outcomes and overall survival were compared between the two groups using cumulative incidence curves and Kaplan–Meier analyses. Normal FEV1 and FVC in this analysis were >80% predicted. RESULTS/ANTICIPATED RESULTS: Thirty-seven cases who had undergone HCT were matched with 74 controls who continued with standard medical therapy. The median age was 8 years for both groups and 59% were females. The median disease severity score was 2 in both groups. At baseline, 70.3% of the HCT group completed pulmonary function tests (PFTs) compared to 35.1% of the non-HCT group. Of these, 73% in both groups had a normal FEV1. In terms of FVC, 57.7% of HCT patients and 76.9% of non-HCT patients had a normal FVC pre-HCT. At 5 years post-HCT, 56.8% of the HCT group had PFTs completed compared to 21.6% of the non-HCT group. Among these, 85.7% in the HCT group had a normal FEV1 compared to 75% in the non-HCT group, while 90.6% had a normal FVC in the HCT group compared to 75% in the non-HCT group. Two of 37 in the HCT group and 1 of 74 in the non-HCT group died ($p = 0.21$). DISCUSSION/SIGNIFICANCE OF IMPACT: Our data suggest that post-HCT, the proportion of patients falling in the normal range for FEV1 and FVC increases. This increase is not seen in the non-HCT group, indicating that HCT may improve this organ function. There was no difference in survival between the groups, indicating the risk of HCT mortality may not be greater than the risk of living with SCD.

521

Evaluation of CXCR4 inhibition with dual checkpoint inhibitor using in vivo and ex vivo models of human and mouse pancreatic cancer

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OBJECTIVES/GOALS: Pancreatic ductal adenocarcinoma (PDAC) is a deadly disease with a mean survival of only 11 months even with the most advanced treatment to date. The desmoplastic microenvironment of PDA is thought to play a critical role in therapy resistance. One pathway that might be responsible for resistance to immunotherapy is the CXCR4-CXCL12 axis. METHODS/STUDY POPULATION: In this study, we propose to evaluate the effect of CXCR4-CXCL12 inhibition on dual checkpoint inhibition in KPC mouse model of PDAC and patient-derived explants. PDAC mouse models are made with pancreatic cancer cells driven by loss of TP53 and activation of KRAS. These models are treated with PD1 inhibitor Balstilimab and an FC-modified CTLA4 Botensilimab with or without CXCR4 inhibitor BL8040. In addition, we make explants of patient tumors along with their tumors and autologous peripheral blood mononuclear cells and this model is similarly challenged with BOT/BAL and BL8040. Using immunofluorescence and flow cytometry, we quantify and evaluate the spatial relationships between different cell populations. Most notably, we evaluate the relative abundance of CD8+ T cells in control and treated conditions. RESULTS/ANTICIPATED RESULTS: We expect the inhibition of CXCR4-CXCL12 axis, along with two new potent checkpoint blockers, will lead to infiltration of CD8+ T cells in both the mouse and human PDAC models. We also expect this to translate into more tumor cell killing as demonstrated by Caspase activities and tumor shrinkage. DISCUSSION/SIGNIFICANCE OF IMPACT: If our hypothesis is proven in both mouse and human PDAC models, this study will serve as a basis for a phase I/II clinical trial testing this combination of drug.

522

CNS complications in women living with HIV: The role of mitochondrial function

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OBJECTIVES/GOALS: As life expectancy increases in people with HIV, neurocognitive impairment is becoming more common, and women with HIV (WWH) are disproportionately impacted. This work investigated mitochondrial function and oxidative stress in WWH in order to understand the relationship between mitochondrial function and cognition in future studies. METHODS/STUDY POPULATION: Peripheral blood mononuclear cells were isolated from virally suppressed WWH (n = 64) and underwent the Seahorse Cell Mito Stress test to assess different realms of mitochondrial function. Cells were then lysed for direct DNA extraction, and quantitative PCR was performed to understand mitochondrial DNA expression (mtDNA) levels as a measure of oxidative stress. A series of simple linear regressions was then conducted to understand the relationships between mitochondrial function and mtDNA content. Future work will expand this analysis to investigate associations between demographic dynamics, such as trauma history, and mitochondrial function, as well as to understand the relationships between mitochondrial function and cognitive outcomes in WWH. RESULTS/ANTICIPATED RESULTS: In our cross-sectional analysis of mitochondrial dynamics in WWH, we found a significant association between maximum mitochondrial respiration ability and mtDNA content, with greater mtDNA expression associated with increased levels of maximum respiration following stimulation. There was no association between basal respiration and levels of oxidative stress. There was also a significant variation in mitochondrial function in our participants, indicating that future analyses to investigate the source of that variation are warranted. The work presented here sheds light on mitochondrial dynamics in WWH and will be the basis for future studies that will investigate how demographic dynamics may be associated with mitochondrial function, as well as how mitochondrial dynamics may predict cognitive outcomes. DISCUSSION/SIGNIFICANCE OF IMPACT: There is significant variation in mitochondrial function in WWH. More analysis is needed to understand what may be associated with these variations, including an investigation of both clinical factors as well as cognitive outcomes. This analysis will inform directions for future mechanistic work aimed at mitigating adverse cognitive outcomes in WWH.

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