HEME OXYGENASE INDUCERS WITH ANTI-PD1 ANTIBODY FOR TUMOR CONTROL OF MURINE PLEURAL MESOTHELIOMA

Lyna Dinh, Joann Miller, Shirron Carter, Min Yuan, Keith Cengel, Theresa Busch

Abstract

Murine pleural mesothelioma, an aggressive and inflammatory cancer, remains challenging to diagnose and treat, with a median survival time of up to one year. Preliminary data suggest that heme oxygenase-1 (HO-1) inducers, such as 5-aminolevulinic acid (5-ALA) and Photofrin, can control murine mesothelioma tumors, offering therapeutic benefits. While HO-1's antioxidant properties may impede traditional cancer treatments, its anti-inflammatory benefits are significant for treating inflammatory diseases like mesothelioma. This study investigates the therapeutic potential of HO-1 inducers in combination with iron supplementation and immunotherapy as hypothesized mechanisms to augment the immune response of mesothelioma tumors. Ferrous drugs produced minimal improvements in efficacy and could induce significant toxicity, with many mice losing 10-15% of their original weight. Conversely, the addition of immunotherapy to a regimen of 500 mg/kg 5-ALA every other day demonstrated superior tumor control compared to controls ($p = 0.002$) and immunotherapy alone ($p = 0.011$). Additionally, combining Photofrin with immunotherapy showed enhanced tumor control over Photofrin alone ($p = 0.0018$), immunotherapy alone ($p = 0.0014$), and controls ($p = 0.0001$). These findings suggest that HO-1 inducers, particularly when used with immunotherapy, may offer a novel approach to treating highly inflammatory cancers such as mesothelioma.

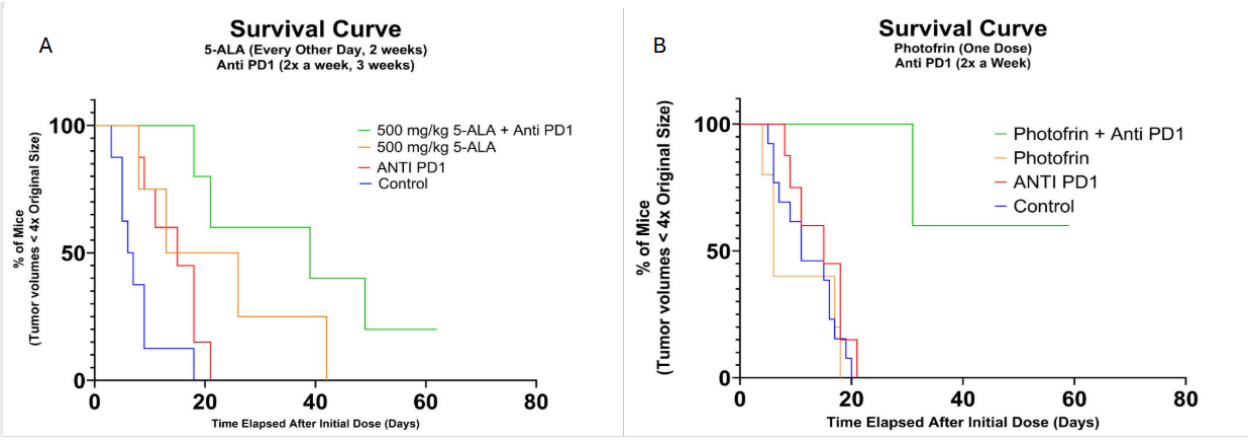

Figure 1: Tumor response of mice receiving immunotherapy with HO-1 inducers. (A) 5-ALA was delivered every other day for two weeks during the same period in which anti-PD1 was delivered twice a week for 3 weeks. Kaplan Meier curves plot mice treated with 500 mg/kg 5-ALA and anti pd1 (N=5); 500 mg/kg 5-ALA (N=6); anti-PD1 alone (N=6) or as untreated controls (N=8). Endpoint is 4x the original tumor volume. (B) Kaplan Meier plots show mice that received a single dose (1 mg/kg) of Photofrin and anti-PD-1 twice a week for 3 weeks(n=5); mice treated with a single dose (1 mg/kg) Photofrin alone (N=5); mice receiving anti PD-1 alone (N=8); and untreated, tumor-bearing mice as controls (N=13). Endpoint is 4x the original tumor volume.