Targeted Administration of Lactate Dehydrogenase Inhibitor during Transarterial Embolization of Target Hepatocellular Carcinomas in a Rat Model

Ryan Baron, B.S.
Medical Student - Drexel University College of Medicine
UPenn PIGI Lab Member

Introduction: Despite improvements in locoregional therapy, recurrence of hepatocellular carcinoma (HCC) remains common, as tumor cells can respond to therapy by undergoing metabolic reprogramming to utilize anaerobic glycolytic pathways via lactate dehydrogenase. In this work, we assessed the growth rates and recurrence rates of HCC in target tumors undergoing transarterial embolization (TAE) with an LDH inhibitor (LDHi), bland TAE (BLAND), and sham therapy (SHAM).

Methods and Materials: Development of autochthonous HCC was induced in 30 Wistar rats using DEN and tumor progressions were tracked with serial MRI until the target tumor reached a volume of 100-300 mm^3. TAE with LDHi were performed using sequential administration of 10 µg/kg LDHi followed by 40-120 µm Embosphere (Merit Medical Systems) (n=12), while bland TAE were performed using Embosphere alone (n=11). An additional cohort underwent a sham TAE procedure without the administration of Embosphere (n=7). Following surgery, rats were serially imaged using T2 MRI, where tumor growth was tracked and monitored for treatment response and potential recurrence. Rats were classified as progressive disease (PD) if there was no decrease in tumor volume by <20%, PR if tumor volume decreased by >20%, and CR if the tumor was eradicated. Recurrence following PR was classified by a >20% increase in tumor volume from the lowest post-treatment volume. Progression free survival was defined as the time to death with no recurrence or the time from treatment to recurrence.

Results: LDHi target tumors had an average %change in tumor volume of -72% from treatment volume, while the BLAND showed a -29% decrease ($p=0.0176$). Results of a Kaplan-Meier survival analysis with a log-rank test showed a significant difference in local progression free survival between the groups ($p<0.0001$). the results of a pairwise log rank analysis administration of LDHi during TAE significantly improved progression free survival as compared to BLAND TAE alone ($p = 0.0352$). All SHAM rats showed no response to treatment and were classified as PD. Treatment responses in the BLAND cohort were 4/11 PD and 7/11 PR, while responses in the LDHi cohort were 1/12 PD, 8/12 PR, and 4/12 CR. The LDHi cohort was the only cohort to achieve local complete response in the targeted tumor.

Conclusion: Administration of LDHi during TAE yields a significantly larger decrease in targeted tumor volume as compared to BLAND TAE, while also providing a statistically significant improvement in progression free survival.