THIRD DDW CONFERENCE – BUDAPEST: Deuterium Depletion & Cancer Treatment
KEYNOTE PRESENTATION

Non-toxic metabolic management of metastatic cancer: Novel combination of ketogenic diet, ketone supplementation, and hyperbaric oxygen therapy

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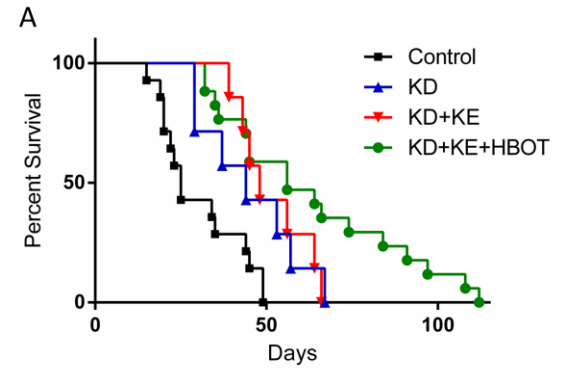
Emerging evidence indicates that cancer is primarily a metabolic disease involving disturbances in energy production. The Warburg effect and tumor hypoxia underlie a unique cancer metabolic phenotype characterized by glucose dependency and aerobic fermentation, which correlate strongly with aggressive capacity and invasive potential [1,3,4,6,7]. The genomic instability observed in tumor cells and all other recognized hallmarks of cancer are considered downstream epiphenomena of the initial disturbance of cellular energy metabolism. Interest in cancer metabolism has increased over the past decade, with researchers suggesting numerous causes and consequences of the Warburg effect (1), and investigating novel therapeutic strategies to exploit this metabolic defect [1-5]. We previously showed that two non-toxic metabolic therapies – the ketogenic diet (KD) with concurrent hyperbaric oxygen (KD+HBOT) and dietary ketone ester supplementation (KE) – could increase survival time in the VM-M3 mouse model of metastatic cancer (8,9). The KD is a low carbohydrate, high fat diet which decreases blood glucose, suppresses insulin and elevates blood ketones, a metabolic fuel that cancer cells cannot use for energy due to mitochondrial defects. Hyperbaric oxygen therapy (HBO_2T) saturates tumors with oxygen, reversing the cancer promoting effects of tumor hypoxia. We hypothesized that combining these therapies could provide an even greater therapeutic benefit in this model by enhancing mitochondrial oxidative phosphorylation. Mice receiving the combination therapy demonstrated a marked reduction in tumor growth rate and metastatic spread, and lived twice as long as control animals. Figure 1 (A,B) shows a Kaplan-Meier survival curve of study groups; note that KD, KD+KE, and KD+KE+HBOT treated mice demonstrated prolonged survival

compared to control high carbohydrate standard diet (SD) ($p=0.03$, $p=0.009$, and $p<0.0001$, respectively; log-rank Mantel-Cox test for survival distribution). To further understand the effects of these metabolic therapies, we characterized the effects of high glucose (control), low glucose (LG), ketone supplementation (βHB), hyperbaric oxygen (HBOT), or combination therapy (LG+βHB+HBOT) on VM-M3 glioma cells. Individually and combined, these metabolic therapies significantly decreased VM-M3 cell proliferation and viability. HBOT, alone or in combination with LG and βHB, increased ROS production in VM-M3 cells. In addition to this work, a number of case reports, human clinical trials and studies in canines with advanced cancer are showing positive results and in some cases complete remission. Our data in animal models and emerging evidence in humans suggests that these metabolic therapies that enhance mitochondrial oxidative phosphorylation should be further investigated as potential non-toxic treatments to replace or complement standard care for patients with systemic metastatic disease.

Figure 1:

A



B

Treatment	Cohort Size	Mean Survival (days)	% Increase in Survival Time
Control (SD)	13	31.2	
KD	7	45.1	44.6*
KD+KE	7	51.6	65.4**
KD+KE+HBOT	17	63.4	103.2***

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KEY WORDS: Warburg effect, cancer metabolism, ketogenic diet, ketone, ketosis, hyperbaric oxygen therapy, metastasis, metastatic cancer

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