LTBK-05. OUTCOMES OF INFANTS AND YOUNG CHILDREN WITH NEWLY DIAGNOSED LOCALIZED (M0) SHH MEDULLOBLASTOMA TREATED ON THE NEXT CONSORTIUM "HEAD START" 4 PROTOCOL

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Advances in RNA and DNA profiling have identified four core molecular subgroups of medulloblastoma of prognostic significance: Sonic Hedgehog (SHH) subtype, WNT subtype, Group 3, and Group 4. Infants and young children with SHH medulloblastoma have demonstrated a favorable outcome in clinical trials utilizing either high-dose chemotherapy ("Head Start") or a combination of intravenous and intraventricular methotrexate (HIT-SKK). Two recently conducted clinical trials (COG ACNS1221 and St. Jude – SJYC07) failed to demonstrate similar survival advantage with conventional dose chemotherapy and without intraventricular methotrexate. "Head Start" 4 (HS 4) is a prospective randomized clinical trial that tailors treatment based on medulloblastoma molecular subgroups and response to induction chemotherapy to compare the efficacy of one versus versus three (tandem) cycles of myeloablative therapy. Eligibility includes newly diagnosed children less than six years of age with localized medulloblastoma. Eligible patients with SHH medulloblastoma were considered "low-risk" and non-randomly assigned to receive three cycles of induction chemotherapy (vincristine, cisplatin, cyclophosphamide, etoposide, and high-dose methotrexate) followed by consolidation with single cycle of myeloablative chemotherapy (thiotepa, carboplatin, etoposide) and autologous hematopoietic progenitor cell rescue. Patients with less than a complete response after three induction cycles received two additional cycles prior to consolidation therapy. Only children between 6 -10 years old, or those with confirmed residual tumor post-consolidation, were meant to receive irradiation after consolidation. Twenty-eight children with localized SHH medulloblastoma were enrolled on the trial with a median age of 2.1 years (range: 0.3-5.9 years). Median follow-up for this cohort is 29.6 months (range: 7.0-58.6 months). The estimated 3-year event-free (EFS) and overall survival (OS) is 96% (CI: 89-100%) and 100%, respectively. The estimated 3-year EFS for SHH subtype 1 and 2 patients is 100% and 95%, respectively (p=0.65). None of the M0 SHH medulloblastoma patients received irradiation.

LTBK-06. MEMANTINE INCREASES DENDRITIC ARBORIZATION AND INTEGRATION OF IMMATURE NEURONS AFTER CRANIAL IRRADIATION

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Cranial irradiation (IR) is a cornerstone in the treatment of high-grade pediatric brain tumors. While lifesaving, it is associated with severe sequalae in 50-90 % of the survivors, as they often show disabling cognitive dysfunction, declined IQ, impaired processing speed, anxiety and posttraumatic stress symptoms, resulting in poorer academic accomplishments and social isolation. Memantine (Mem) is a non-competitive NMDA receptor antagonist and a potent enhancer of neural plasticity. It is used in the clinical setting in the treatment of Alzheimer's disease and dementias and has been shown to enhance cognition in post-IR cancer survivors. Nevertheless, while an improvement in synaptic plasticity has been documented in association to hippocampal neurogenesis, the exact mechanisms underlying Mem's actions are yet poorly understood. The goal of this project is to further dissect the actions of Mem and identify factors that contribute to hippocampal neurogenesis. To this end, 20-day-old C57BL6/J mice were subjected to a single dose of 7 Gy whole brain irradiation and then supplied with Mem in the drinking water to obtain a steady-state plasma concentration of the drug. Animals were then sacrificed at different time points and the brains harvested for immunohistochemical staining, bulk-RNA sequencing and electrophysiological studies. Sholl analysis of the morphological data of the new-born neurons of Mem treated animals showed a statistically significant increase in coverage area (500µm2 vs. 250µm2, p= <0,0001) and number of dendrites (15 vs. 5, p= <0,0001) compared to non-treated individuals. Preliminary analysis of the electrophysiological responses revealed no changes in the gamma oscillations in Mem treated irradiated mice. The attained results will shed light on the mechanisms of action and take steps towards establishing Mem as a neoadjuvant therapy for children undergoing IR. Ultimately, we aim to ameliorate IR-associated neurocognitive impairment and improve the quality of life of pediatric cancer survivors.