EMBR-28. CNS DISTRIBUTIONAL KINETICS OF PANOBINOSTAT IN THE MOUSE

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Medulloblastoma (MB) is the most common malignant pediatric brain tumor and has the potential for leptomeningeal spread, often responsible for the preponderance of morbidity and mortality in MB patients. Adverse sequelae following high dose craniospinal radiation and aggressive chemotherapies, including neurocognitive deficits and endocrine disorders, impairs patient quality of life and thus call for new therapeutic strategies. Panobinostat is a pan-histone deacetylase (HDAC) inhibitor that has been shown to be effective against MBs *in vitro*. The objective of the current study is to evaluate the key pharmacokinetic (PK) parameters and the mechanisms influencing the brain penetration of panobinostat in the mouse model, often used in MB preclinical efficacy trials. Pharmacokinetic studies were conducted using FVB wild-type (WT) mice and triple-knockout (TKO, Mdr1a/b$^{-/-}$Bcrp1$^{-/-}$) transporter-deficient mice. Panobinostat was administered intravenously (10 mg/kg) and concentrations at selected time points in plasma, brain and spinal cord were determined using LC-MS/MS. PK parameters, including systemic clearances, volumes of distribution, half-lives, and areas-under-the-concentration time curve (AUC) were calculated by using non-compartmental analysis. In WT mice, the CNS penetration was initially limited; however, it increased with time and the brain-to-plasma (B/P) and spinal cord-to-plasma (SC/P) distributional partition coefficients (AUC ratios) were 3.7 and 1.4, respectively. The B/P and SC/P ratios of panobinostat in BBB transporter-deficient TKO mice were 1.7- and 2.3-fold higher than those in WT mice, respectively. Our data suggest that P-glycoprotein (P-gp) and/or breast cancer resistance protein (Bcrp) efflux transporters, localized in BBB, may influence the delivery of panobinostat to tumors in the brain following systemic intravenous administration. These systemic and CNS distributional parameters will inform future preclinical efficacy studies of panobinostat for MB. As such, studies investigating other administration routes that can bypass the BBB, such as the intrathecal injection of novel formulations, are ongoing.

EMBR-29. PEDIATRIC MEDULLOBLASTOMA PATIENT WITH MULTIPLE MIDLINE DEFECTS, A CASE REPORT

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Medulloblastoma (MB) is the most common malignant central nervous system (CNS) cancer diagnosed in childhood and is divided into four subtypes: WNT-activated, SHH-activated, Group 3 (Non-WNT, Non-SHH), and Group 4 (Non-WNT, Non-SHH). Non-WNT/Non-SHH make up roughly two-thirds of MB and have the least understood pathogenesis with substantial intratumoral heterogeneity. Therapeutic targets and treatment strategies for Group 3 and 4 patients therefore remain unclear. In this report we present a 16-year-old patient with standard risk Group 4 medulloblastoma and multiple midline defects. The patient's medical history was remarkable for a cleft lip (which healed in utero), a notable heart murmur, an inguinal hernia repair at 3 months of age, and significant pectus excavatum. This patient was diagnosed at age 12 with a MB. Tumor cells were negative for GAB-1, p53 stain was positive for approximately 1–2% of tumor cells, no evidence on monosomy 6, MYC or MYCN amplification. The family history is significant for paternal biliary cancer. The patient was treated as per ACNS0331 and is approximately 36 months off-therapy. This case presents an interesting instance of a CNS tumor arising within the microenvironment of wide-spread dysregulated development. Single cases do not provide any substantiative evidence. However, they do give insight on factors which may drive oncogenesis and may provide an indication as to whether we should continue to pursue targeted therapy for Group 3/4 uniformly or move towards personalized therapy strategies in this group patients.

EMBR-30. A NOVEL PLK1 INHIBITOR ONVANSERTIB EFFECTIVELY SENSITIZES GROUP 3 MEDULLOBLASTOMA TO RADIOTHERAPY

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Medulloblastoma (MB) is often accompanied by MYC amplification. PLK1 is an oncogenic kinase that controls cell cycle and proliferation, and it has been preclinically validated as a cancer therapeutic target. Onvansertib (PCM-075) is a novel, orally available PLK1 inhibitor, which shows tumor growth inhibition in many types of cancer. We examined the effect of Onvansertib on MYC-driven medulloblastoma as a monotherapy or in combination with radiation. A Crisper-Cas9 screen was used to discover essential genes for MB tumor growth. Microarray and immunohistochemistry on pediatric patient samples were performed to examine the expression of PLK1. The effect of Onvansertib *in vitro* was measure by cell viability, colony-forming assays, extreme limiting dilution assay, and RNA-Seq. ALDH activity, cell-cycle distribution, and apoptosis were analyzed by flow cytometry. DNA damage was assessed by immunofluorescence staining. Medulloblastoma xenografts were generated to explore the monotherapy or radio-sensitizing effect. PLK1 is overexpressed in Group 3 MB. The IC50 concentrations of Onvansertib in Group 3 MB cell lines were between 4.9 and 6 nM. Onvansertib reduced colony formation, cell proliferation, stem cell renewal, and induced G2/M arrest *in vitro*. Moreover, Onvansertib in combination with radiation increased DNA damage and apoptosis compared with radiation alone. The combination of Onvansertib with radiotherapy resulted in marked tumor regression in orthotopic xenografts. These findings suggest that Onvansertib is an effective strategy in combination with radiotherapy in MB.

EMBR-31. DEVELOPMENT OF INJECTABLE POLYSACCHARIDE HYDROGEL TO ENHANCE DRUG PENETRATION IN PEDIATRIC BRAIN TUMORS

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Improving unacceptable low response rates and reducing acute and long-term morbidities remain significant challenges in pediatric neuro-oncology. Chemotherapy is an effective primary or adjuvant treatment for pediatric disease, but current administration approaches hinder the pharmacological activity exerted by chemotherapy treatments. Barriers in the route of drug administration and in the tumor microenvironment limit anticancer drugs from penetrating tissue efficiently and reaching all cancer cells. Strategies have been proposed to overcome these barriers with hope of leading to sustained and elongated drug exposure in solid tumors. However, few methods have been explored to design drug delivery systems to circumvent these barriers with potential to enhance drug penetration and reduce adverse systemic side effects in treating pediatric brain tumors. In this study, we validate an injectable polysaccharide hydrogel capable of releasing drugs locally at tumor site, sustaining drug concentration, and eliciting tumor response. We synthesized a hydrogel with dimethyl sulfoxide (DMSO) incorporating amylopectin, a polysaccharide found in starch, loaded with doxorubicin. We determined the structure of doxorubicin is not altered when released from the hydrogel through characterization of drug-loaded and unloaded hydrogels, suggesting drug is encapsulated in the hydrogel network and is able to maintain structure to induce mechanism of action. We tested sustained release of drug and therapeutic efficacy in vitro with DAOY, a medulloblastoma cell line. Our approach demonstrates that local drug delivery presents potential to enhance drug penetration in pediatric brain tumors by sustaining drug concentration at tumor site for an extended period of time. Local drug delivery systems have been investigated for decades but few have been investigated for treatment of pediatric brain tumors. For researchers, physicians, and clinicians, this research can lead to a greater effort to improve current outcomes of conventional drug treatment and provide an opportunity to address current challenges in pediatric oncology.

EMBR-32. INTEGRATED STRESS RESPONSE PLAYS A PRO-SURVIVAL ROLE IN MYC-DRIVEN MEDULLOBLASTOMA

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Medulloblastoma (MB) accounts for 20% of diagnosed brain tumors in children. Group 3 (G3) MB subtype is the most aggressive. Molecularly, G3 MB is characterized by MYC overexpression, which drives elevated mRNA translation in tumor cells. PERK is an eukaryotic translation initiation factor 2 (eIF2α) kinase that inhibits mRNA translation under endoplasmic reticulum (ER) stress conditions, such as in response to accumulation of unfolded proteins. When unfolded proteins accumulate in the ER, activated PERK phosphorylates eIF2α. This shuts down global translation and triggers integrated stress response (ISR) to help cells adapt through selective translation of mRNA encoding pro-survival proteins. High mRNA expression of PERK correlates with poor survival in G3 MB patients. In vitro, combination of ER or hypoxic stress with PERK knockdown induces apoptosis in MB cells. ISRIB is an ISR inhibitor that maintains translation rates despite eIF2α phosphorylation. Combining ISRIB with stress such as hypoxia induces apoptosis in MB cells and prevents accumulation of key ISR mediators such as ATF4. In addition, combination of ISRIB and hypoxia induces oxidative stress. Current G3 MB treatment regimens include vincristine, a known ISR inducer. Combination of ISRIB with vincristine amplifies vincristine-induced apoptosis, potentially suggesting novel therapeutic approach for MB. Our findings show that inhibition of ISR in G3 MB represents a powerful inducer of cancer cell death.