doses of topotecan (1-87/patient, mean 23, median 18) were administered at our department. Treatment was given over a period of 0-65 months (mean and median 33 months). Intraventricular treatment with topotecan was generally well tolerated. Two patients reported side effects. One boy with multiple recurrences of an ependymoma in the posterior fossa showed increased tremor after intraventricular administration of topotecan, another girl with recurrent medulloblastoma reported fatigue. CONCLUSION: Intraventricular therapy with topotecan is feasible and generally well tolerated. Topotecan can be an important addition for patients with recurrent malignant brain tumors to increase cytotoxic drug concentrations in CSF.

DDEL-06. DRUG DELIVERY TO THE PONS USING SHORT-PULSE FOCUSED ULTRASOUND AND MICROBUBBLE EXPOSURE FOR THE TREATMENT OF DIFFUSE MIDLINE GLIOMA

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Despite advances in understanding diffuse midline glioma (DMG-H3K27), including DIPG, there are still no effective treatments available, and the dismal clinical prognosis remains. This is partly because of tumour spread behind an intact blood brain barrier (BBB), preventing drug delivery and the reason for many drugs failing in the clinic. The use of focused ultrasound and intravenous microbubbles enables temporary increases in BBB permeability, allowing drugs to enter the targeted brain region. Building on recent research demonstrating that short pulses (<5 μs) of ultrasound can deliver drugs safely and uniformly to the hippocampus, we evaluated whether a similar result was achievable in the pons of mice. Mice were exposed to ultrasound (peak-negative pressure: 0.4 MPa, pulse length: 5 cycles, centre frequency 1 MHz) emitted in bursts of 38 pulses. During exposure mice received an intravenous injection of SonoVue(R) microbubbles and a fluorescently-tagged tracer (dextran, 3 kDa), acting as a drug mimic. Dextran was successfully delivered to the pons of non-tumour-bearing mice assessed by fluorescence microscopy immediately post-treatment. Dextran delivery was repeatable and confined to the targeted pons region with a homogenous distribution, typical of short pulse ultrasound, and important for treating DMG to ensure all tumour cells receive an equal drug dose. No damage to the brain was observed after H&E staining. Panobinostat has shown promise in vitro but tolerated doses have not shown therapeutic benefit in vivo as it does not cross the BBB. The in vitro toxicity of panobinostat was confirmed in a Nestin-Tv-a/p53fl/fl, RCAS-ACVR1R206H + RCAS-H3.1K27M murine cell line, with a GI_{50} of 15.56 nM. The ability of focused ultrasound to deliver panobinostat across the BBB to these tumours grown orthotopically will be assessed. Overall, we hope to develop a drug delivery system, that enables therapeutics to cross the BBB, expanding treatment options for DMG.

DDEL-07. A PHASE I STUDY EXAMINING THE FEASIBILITY OF INTERMITTENT CONVECTION-ENHANCED DELIVERY (CED) OF MTX110 FOR THE TREATMENT OF CHILDREN WITH NEWLY DIAGNOSED DIFFUSE MIDLINE GLIOMAS (DMGS)

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Histone deacetylase inhibitors have been found preclinically to be among the most active agents against DMGs, however, they are clinically ineffective with systemic delivery due to blood brain barrier limitations and toxicity. Using a repurposed device (implantable subcutaneous pump connected with a catheter directly implanted into the pons/thalamus) we are performing a phase I, standard 3 + 3 dose escalation study to investigate the safety and feasibility of repeated infusions of MTX110 (Midatech Pharma), a water-soluble formulation of panobinostat, via CED. Eligible patents are between 3 and 18 years of age with newly diagnosed DMG following radiation therapy, without hemorrhage or cyst in the tumor, and having intact organ function. Following tumor biopsy and device implantation, patients receive two 48-hour-infusion pulses 7 days apart of MTX110 (30, 60, or 90 mM). The infusion pump is prefilled with MTX110 (and gadolinium for co-infusion to serve as a surrogate for drug distribution) and administered using the wireless N'Vision clinical programmer at a rate of 0.2 mL/hr. Seven patients (30 mM group, n=3 and 60 mM group, n=4) have been treated with the MTX110 infusate. All but one patient had adequate tumor coverage as measured by co-infused gadolinium on MRI. One patient suffered a severe adverse event related to the infusion and tumor anatomy. Four patients had Grade 2 transient neurological deficits related to biopsy (n=1) and the infusion (n=3). In a follow up period of 12-22 months from diagnosis, progression free survival ranges from 8 to 20 months. With one objective response, 3 patients remain alive (2 without progression, both at 12 months, and 1 with progressive disease, at 22 months post diagnosis). Three patients are expected to be treated at 90 mM level. Using MTX110, we demonstrated the safety and feasibility of repeated drug infusion by CED in DMG patients.

EARLY PHASE CLINICAL TRIALS

EPCT-01. PEDIATRIC BRAIN TUMOR CONSORTIUM (PBTC)-055: A PHASE I STUDY OF TRAMETINIB AND HYDROXYCHLOROQUINE (HCQ) FOR BRAF-FUSION OR NEUROFIBROMATOSIS TYPE-1 (NF1)-ASSOCIATED PEDIATRIC GLIOMAS

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INTRODUCTION: Autophagy is a highly conserved process by which intracellular components are degraded and recycled promoting cell survival. Preclinically, autophagy has been implicated as a resistance mechanism in BRAF-mutant glioma cells treated with MAPK-pathway inhibitors. HCQ, an oral autophagy inhibitor, has been evaluated preclinically and clinically to overcome resistance. METHODS: PBTC-055 (NCT04201457) is a phase I/II trial of HCQ combined with trametinib (BRAF-fusion or NF1-associated gliomas) or trametinib and dabrafenib (BRAFV600E gliomas) in patients < 30 years with progressive glioma. Prior treatment with RAF and/or MEK inhibitor with sub-optimal response (no response or response followed by progression on therapy) was required. Here, we present phase I data combining trametinib with HCQ utilizing a rolling-6 design. HCQ was administered at escalating dose levels (8, 15, or 20 mg/kg/day divided BID) in combination with standard pediatric trametinib dosing. All patients received prior MEK inhibitor therapy; 5/18 (28%) exhibited no response and 13/18 (72%) progressed on active therapy. RESULTS: Eighteen eligible/evaluable subjects were enrolled. Median age was 9.6 years (2.5-20.4 years); 10 were male. There were 2 dose-limiting toxicities (both grade 3 rash one each at DL1 and DL3). The highest dose level of HCQ (20 mg/kg/day divided BID) was declared the RP2D. Grade 3 adverse events possibly related to therapy included skin infection, rash, cardiac ejection fraction decrease, weight loss, and anorexia. There were no grade 4 or 5 attributable toxicities. Preliminarily, combination pharmacokinetic assessment revealed similar metabolism of trametinib to that reported as a single agent; HCQ demonstrated more rapid clearance compared to adults. Pharmacodynamic assessments are ongoing. CONCLUSIONS: The combination of trametinib and HCQ is safe with a RP2D of HCQ of 20 mg/kg/day divided BID. Currently, subjects are enrolling on the phase II portion evaluating the efficacy of this novel combination.

EPCT-02. A PHASE 1 STUDY OF MEBENDAZOLE WITH BEVACIZUMAB AND IRINOTECAN IN HIGH GRADE GLIOMAS

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BACKGROUND: High grade gliomas (HGG) have a dismal prognosis despite multimodal therapy. Mebendazole (MBZ) is an anti-helminthic benzimidazole. In vitro, MBZ has efficacy in numerous cancer models and is able to cross the blood brain barrier. We conducted a phase 1 trial (NCT01837862) to evaluate the safety of MBZ in combination with bevacizumab (BVCZ) and irinotecan (CPT-11). OBJECTIVE: To determine the maximally tolerated dose of MBZ when given in combination with BVCZ and CPT-11 in children with high-grade gliomas; to describe the progression-free survival (PFS) and overall survival (OS) for this group. METHODS: Patients between 1 and 21 years of age with HGG were enrolled in a 3 + 3 design to escalating doses of MBZ in combination with BVCZ 10mg/kg/dose and CPT-11 150mg/m2/dose. Subjects were eligible upfront after completion of radiation or at the time of progression. MBZ was taken orally twice per day continuously and BVCZ and CPT-11 were given intravenously on days