tent of resection (EOR) and its impact on survival, with particular consideration of EOR in relation to the four MB consensus molecular subgroups (WNT, SHH, Group 3, Group 4). We collected data from 1113 patients (n=419, UK CCLG institutions; n=694, published data) representing the largest ever combined cohort constructed to assess the impact of EOR in medulloblastoma. We performed association analyses and univariate/multivariate survival analysis using Kaplan-Meier, log-rank and Cox proportional hazard modelling, analysing overall survival (OS) cohort-wide and with reference to molecular subgroups and clinical features. Association analysis of the combined cohort evidenced that infant patients were more likely to have STR (p=0.02). In this whole-cohort analysis, EOR was significantly associated with survival in univariate analysis (HR 1.64, 95% CI 1.30-2.07, p=<0.001) but not in multivariate analysis. STR was variably prognostic in sub-cohort analyses of specific demographics and molecular subgroup; worse outcomes were observed in patients <5 years in SHH (p=0.044) and Group 4 (p=0.044). This was true for WNT patients >5 years old at diagnosis (p=0.034) although numbers were small and require validation in even larger cohorts. In this cohort of >1100 MBs, STR was significantly associated with a lower OS in univariate analysis, but this was driven by specific disease contexts (SHH and Group 4 patients <5 years old). STR was not independently prognostic overall or in any setting. We recommended that surgeons should continue to pursue maximal *safe* resection for all MB patients but suggest that consideration of STR as a high-risk feature should be disease context specific.

MEDB-32. REDUCING TREATMENT-RELATED TOXICITY FOR CHILDREN WITH WNT-ACTIVATED MEDULLOBLASTOMA

Jessica Taylor, Joseph Toker, Katherine Masih, Erica Nathan, Sabrina Terranova, Richard Gilbertson; CRUK Cambridge Institute, Cambridge, United Kingdom

WNT-medulloblastoma has an excellent prognosis, with an overall survival rate of 90% among children receiving standard-of-care (SOC) surgical resection, radiotherapy, and chemotherapy. Unfortunately, while curative, this treatment is associated with major, long-term, debilitating motor, developmental, and neuroendocrine side effects. Therefore, it is crucial we develop effective, less toxic therapies for these children. Similarities have been demonstrated between cancer cell lysosomes and those of patients with Niemann-Pick, a lysosomal storage disease characterised by lysosomal fragility and sphingomyelin accumulation. A class of drugs known as Functional Inhibitors of Acid Sphingomyelinase (FIASMAs), increase lysosomal sphingomyelin and destabilise the cancer cell's more fragile lysosomal membrane which leads to the induction of cell-death pathways via lysosomal membrane permeabilisation. Loratadine, an antihistamine with high FIASMA activity, consistently induced lysosomal membrane permeabilisation, leading to increased cell-death, in our panel of mouse and human WNT-medulloblastoma lines. Loratadine exhibited no detrimental effect on normal mouse embryonic stem cells from the lower rhombic lip – the putative cell of origin in WNT-medulloblastoma. Luciferase-expressing mouse WNT-medulloblastoma cells were orthotopically implanted into CD1-nude mice and monitored for tumour development via bioluminescent imaging. Upon tumour engraftment, mice were subjected to reduced SOC (radiotherapy and adjuvant vincristine) plus a clinically relevant dose of loratadine. Response and survival were compared to mice treated with full SOC (radiotherapy, vincristine, cisplatin, and etoposide). Mice treated with 2mg/kg/day of loratadine following reduced SOC demonstrated increased survival when compared to those treated with full SOC (p=0.02) along with a significant reduction in weight loss during treatment (p=<0.0001). This work suggests that loratadine, or other FIASMA compounds, may be good alternative adjuvant therapies for WNT-medulloblastoma. Using less toxic adjuvants could improve long-term outcomes through reducing therapeutic related toxicities for children with this devastating disease.

MEDB-33. THE LANDSCAPE OF ECDNA IN MEDULLOBLASTOMA

Owen Chapman[1], Sunita Sridhar[1,2], Shanqing Wang[1], Jon Larson[3], Robert Wechsler-Reya[3], Jill Mesirov[1], Lukas Chavez[1]; [1]UC San Diego, La Jolla, CA, USA. [2]Rady Children's Hospital, San Diego, CA, USA. [3]Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA

Extrachromosomal circular DNA (ecDNA) is an important driver of aggressive cancers, including medulloblastoma (MB), the most common malignant pediatric brain tumor. To assess the clinical importance of ecDNA in MB, we applied computational methods to detect ecDNA in the genomes of a cohort of 468 MB patients and 31 MB model systems. Among patients, ecDNA was detected in 18% of tumors and carried a threefold greater risk of mortality. Affected genomic loci harbor up to hundredfold amplification of oncogenes including MYC, MYCN, TERT, and other novel putative oncogenes. Between sequential patient biopsies at initial diagnosis and subsequent relapse, we observed structural variation at ecDNA loci and generation of new ecDNA sequences. Among model systems, ecDNA was found in 19 of 31 genomes (61%). Although ecDNA was far more prevalent among MB models than patients, the ecDNA genomic sequences were conserved between most patient-derived xenograft (PDX) models and the human tumors from which they were made. To elucidate the functional regulatory landscapes of ecDNAs in MB, we generated transcriptional (RNA-seq), accessible chromatin (ATAC-seq), and chromatin interaction (Hi-C) profiles of 6 MB tumor samples. In each case, we identified regulatory interactions that cross fusion breakpoints on the ecDNA, representing potential "enhancer rewiring" events which may contribute to transcriptional activation of co-amplified oncogenes. To test this hypothesis, we are currently conducting in vitro CRISPRi screens targeting regulatory regions on the ecDNA of a MB cell line to determine whether these enhancers promote proliferation. Using single-cell sequencing, we have also begun exploring intratumoral heterogeneity of ecDNA in a p53-mutant SHH MB patient tumor and its corresponding PDX model. In summary, our study analyzes the frequency, diversity, and functional relevance of ecDNA across MB subgroups and provides strong justification for continued mechanistic studies of ecDNA in MB with the potential to uncover new therapeutic approaches.

MEDB-34. A VERY RARE CASE: MEDULLOBLASTOMA RELAPSE WITH BONE MARROW INFILTRATION IN A TODDLER

Claudia Zinke[1], Gudrun Fleischhack[2], Julia Hauer[1], Björn Sönke Lange[1], Jenny Dörnemann[1], Gabriele Hahn[3], Gabriele Schackert[4], Kristin Gurtner[5], Matthias Meinhardt[6], Korinna Jöhrens[6], Ralf Knöfler[1]; [1]University Hospital Carl Gustav Carus, Department of Pediatrics, Pediatric Hematology and Oncology, Dresden, Germany. [2]University Hospital of Essen; Department of Pediatrics, Pediatric Hematology and Oncology, Pediatrics III, Essen, Germany. [3]University Hospital Carl Gustav Carus, Department of Diagnostic and Interventional Radiology, Dresden, Germany. [4]University Hospital Carl Gustav Carus, Department of Neurosurgery, Dresden, Germany. [5]University Hospital Carl Gustav Carus, Department of Radiation Therapy and Radiation Oncology, Dresden, Germany. [6]University Hospital Carl Gustav Carus, Department of Pathology, Dresden, Germany

We report about a female toddler congenitally deaf and diagnosed with a non-metastatic desmoplastic medulloblastoma (SHH activated, *TP53*-wt, variant in *LDB1* gene). No tumor predisposition syndrome was found. After complete tumor resection the patient was treated according to I-HIT-MED-Guidance protocol. Five months later an asymptomatic localised relapse (same histology, *PTEN* frameshift deletion, *TERT* mutation, *LDB1* mutation) detected by routine MRI was treated by complete resection, craniospinal irradiation and an antiangiogenic regimen adapted from the MEMMAT scheme including fenofibrate, thalidomide, celecoxib, topotecan, temozolomide, bevacizumab and intraventricular cytarabine. Before start of systemic treatment blood cell counts were normal. In the second cycle we had to interrupt chemotherapy due to a leukopenia while continuing the antiangiogenic treatment. In order to avoid relevant bone marrow toxicity chemotherapy doses were reduced. Nevertheless we had to stop the fourth cycle because of a severe pancytopenia. Same time the girl presented with fever, neck and leg pain. A full blood count showed: hemoglobin 6.92 g/dl, leukocytes 640/µl, platelets 8,000/µl. Suspecting an infection supported by the presence of a high CrP value of 230 mg/l the patient was treated with i.v. antibiotics. MRI showed an unspecific retropharyngeal soft tissue augmentation, a pleural effusion and high T2 signals in multiple vertebral bodies but no central tumor relapse. The bone marrow diagnostics revealed a diffuse medulloblastoma cell infiltration with the known *PTEN* frameshift deletion and *LDB1* mutation. The liquor was tumor-cell free. We report on an extremely rare case of an early local relapse of desmoplastic medulloblastoma progressing to a diffuse bone marrow infiltration in a toddler. The girl died due to therapy resistance 9 weeks after bone marrow relapse. It remains unclear whether the fatal course was related to the hereditary deafness syndrome and the molecular alterations of the tumor.

MEDB-35. RELATIONSHIP BETWEEN GENETIC PROFILE, HISTOLOGY, CLINICAL FEATURES AND LONG-TERM OUTCOME IN YOUNG CHILDREN MEDULLOBLASTOMA (YCMB) TREATED WITH UPFRONT HIGH DOSE CHEMOTHERAPY (HDCT) IN ITALY

Maria Luisa Garrè[1], Maura Massimino[2], Francesca Romana Buttarelli[3], Lorenza Gandola[4], Salvina Barra[5], Felice Giangaspero[3,6], Tobias Goschzik[7], Veronica Biassoni[2], Lorenza Pastorino[8], Angela Pistorio[9], Torsten Pietsch[7]; [1]Neuroncology Unit, IRCCS- Istituto Giannina Gaslini, Genoa, Italy. [2]Pediatric Oncology Unit, Fondazione IRCCS-Istituto Nazionale dei Tumori, Milan, Italy. [3]Department of Radiologic,Oncologic and Anatomopathological Sciences, University La Sapienza, Rome, Italy. [4]Department of Radiation Oncology, Fondazione IRCCS-Istituto Nazionale dei Tumori, Milan, Italy. [5]Radiotherapypy Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy. [6]IRCCS Neuromed, Pozzilli, Isernia, Italy. [7]Department of Neuropathology, University of Bonn Medical Center, Bonn, Germany. [8]Genetics of rare cancers, IRCCS Ospedale Policlinico